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**Henri [FR/FR]; AstraZeneca Reims, Z.I. la Pompelle, BP 1050, F-51689 Reims, Cedex 2 (FR).**

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**(71) Applicant** (for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE,

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**(71) Applicant (for MG only):** **ASTRAZENECA UK LIM-**

ITED [GB/GB]; 15 Stanhope Gate, London Greater London W1K 1LN (GB).

**(72) Inventor; and**

(75) Inventor/Applicant (for US only): JUNG, Frederic.

**(74) Agent: GLOBAL INTELLECTUAL PROPERTY; AstraZeneca AB, S-SE-151 85 Södertälje (SE).**

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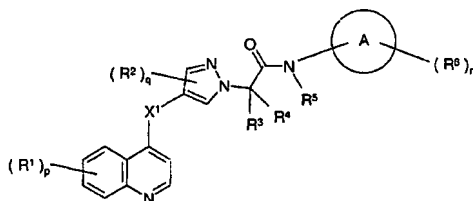
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(54) Title: QUINOLINE DERIVATIVES



(1)

**(57) Abstract:** The invention concerns quinoline derivatives of Formula (I) or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, wherein each of p, R<sup>1</sup>, q, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, Ring A, r and R<sup>6</sup> has any of the meanings defined in the description; processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use in the treatment of cell proliferative disorders or in the treatment of disease states associated with angiogenesis and/or vascular permeability.

**WO 2006/040522 A1**

**QUINOLINE DERIVATIVES**

The invention concerns certain novel quinoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-cancer activity and are  
5 accordingly useful in methods of treatment of the human or animal body. The invention also concerns processes for the manufacture of said quinoline derivatives, to pharmaceutical compositions containing them and to their use in therapeutic methods, for example in the manufacture of medicaments for use in the prevention or treatment of cancers in a warm-blooded animal such as man, including use in the prevention or treatment of solid  
10 tumour disease.

Many of the current treatment regimes for the abnormal cell growth found in cell proliferation diseases such as psoriasis and cancer utilise compounds which inhibit DNA synthesis. Such compounds are toxic to cells generally but their toxic effect on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to anti-cancer  
15 agents which act by mechanisms other than the inhibition of DNA synthesis have the potential to display enhanced selectivity of action.

Eukaryotic cells are continually responding to many diverse extracellular signals that enable communication between cells within an organism. These signals regulate a wide variety of physical responses in the cell including proliferation, differentiation, apoptosis and  
20 motility. The extracellular signals take the form of a diverse variety of soluble factors including growth factors as well as paracrine, autocrine and endocrine factors. By binding to specific transmembrane receptors, growth factor ligands communicate extracellular signals to the intracellular signalling pathways, thereby causing the individual cell to respond to extracellular signals. Many of these signal transduction processes utilise the reversible process  
25 of the phosphorylation of proteins involving specific kinases and phosphatases.

As phosphorylation is such an important regulatory mechanism in the signal transduction process, it is not surprising that aberrations in the process result in abnormal cell differentiation, transformation and growth. For example, it has been discovered that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene.  
30 Several such oncogenes encode proteins which are receptors for growth factors, for example tyrosine kinase enzymes. Tyrosine kinases may also be mutated to constitutively active forms that result in the transformation of a variety of human cells. Alternatively, the over-expression of normal tyrosine kinase enzymes may also result in abnormal cell proliferation.

- 2 -

Tyrosine kinase enzymes may be divided into two groups :- the receptor tyrosine kinases and the non-receptor tyrosine kinases. About 90 tyrosine kinase have been identified in the human genome, of which about 60 are of the receptor type and about 30 are of the non-receptor type. These can be categorised into 20 receptor tyrosine kinase sub-families according to the families of growth factors that they bind and into 10 non-receptor tyrosine kinase sub-families (Robinson *et al*, Oncogene, 2000, 19, 5548-5557). The classification includes the EGF family of receptor tyrosine kinases such as the EGF, TGF $\alpha$ , Neu and erbB receptors, the insulin family of receptor tyrosine kinases such as the insulin and IGF1 receptors and insulin-related receptor (IRR) and the Class III family of receptor tyrosine kinases such as the platelet-derived growth factor (PDGF) receptor tyrosine kinases, for example the PDGF $\alpha$  and PDGF $\beta$  receptors, the stem cell factor receptor tyrosine kinase (SCF RTK (commonly known as c-Kit), the fms-related tyrosine kinase 3 (Flt3) receptor tyrosine kinase and the colony-stimulating factor 1 receptor (CSF-1R) tyrosine kinase.

It has been discovered that such mutated and over-expressed forms of tyrosine kinases are present in a large proportion of common human cancers such as the leukaemias, breast cancer, prostate cancer, non-small cell lung cancer (NSCLC) including adenocarcinomas and squamous cell cancer of the lung, gastrointestinal cancer including colon, rectal and stomach cancer, bladder cancer, oesophageal cancer, ovarian cancer and pancreatic cancer. As further human tumour tissues are tested, it is expected that the widespread prevalence and relevance of tyrosine kinases will be further established. For example, it has been shown that EGFR tyrosine kinase is mutated and/or over-expressed in several human cancers including in tumours of the lung, head and neck, gastrointestinal tract, breast, oesophagus, ovary, uterus, bladder and thyroid.

Platelet-derived growth factor (PDGF) is a major mitogen for connective tissue cells and other cell types. The PDGF receptors comprising PDGF $\alpha$  and PDGF $\beta$  receptor isozymes display enhanced activity in blood vessel disease (for example atherosclerosis and restenosis, for example in the process of restenosis subsequent to balloon angioplasty and heart arterial by-pass surgery). Such enhanced PDGF receptor kinase activity is also observed in other cell proliferative disorders such as fibrotic diseases (for example kidney fibrosis, hepatic cirrhosis, lung fibrosis and multicystic renal dysplasia), glomerulonephritis, inflammatory diseases (for example rheumatoid arthritis and inflammatory bowel disease), multiple sclerosis, psoriasis,

- 3 -

hypersensitivity reactions of the skin, allergic asthma, insulin-dependent diabetes, diabetic retinopathy and diabetic nephropathy.

The PDGF receptors can also contribute to cell transformation in cancers and leukaemias by autocrine stimulation of cell growth. It has been shown that PDGF receptor  
5 kinases are mutated and/or over-expressed in several human cancers including in tumours of the lung (non-small cell lung cancer and small cell lung cancer), gastrointestinal (such as colon, rectal and stomach tumours), prostate, breast, kidney, liver, brain (such as glioblastoma), oesophagus, ovary, pancreas and skin (such as dermatofibrosarcoma protruberans) and in leukaemias and lymphomas such as chronic myelogenous leukaemia (CML), chronic  
10 myelomonocytic leukaemia (CMML), acute lymphocyte leukaemia (ALL) and multiple myeloma. Enhanced cell signalling by way of the PDGF receptor tyrosine kinases can contribute to a variety of cellular effects including cell proliferation, cellular mobility and invasiveness, cell permeability and cellular apoptosis.

Accordingly, antagonism of the activity of PDGF receptor kinases is expected to be  
15 beneficial in the treatment of a number of cell proliferative disorders such as cancer, especially in inhibiting tumour growth and metastasis and in inhibiting the progression of leukaemia.

In addition, PDGF is involved in angiogenesis, the process of forming new blood vessels, that is critical for continuing tumour growth. Normally, angiogenesis plays an important role in processes such as embryonic development, wound healing and several  
20 components of female reproductive function. However, undesirable or pathological angiogenesis has been associated with a number of disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma. Angiogenesis is stimulated *via* the promotion of the growth of endothelial cells. Several polypeptides with *in vitro* endothelial cell growth promoting activity have been identified  
25 including acidic and basic fibroblast growth factors (aFGF and bFGF) and vascular endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor activity of VEGF, in contrast to that of aFGF and bFGF, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis and vascular permeability. This cytokine induces a  
30 vascular sprouting phenotype by inducing endothelial cell proliferation, protease expression and migration which subsequently leads to the formation of capillary tubes that promote the formation of the hyperpermeable, immature vascular network which is characteristic of pathological angiogenesis. The receptor tyrosine kinase (RTK) sub-family that binds VEGF

- 4 -

comprises the kinase insert domain-containing receptor KDR (also referred to as Flk-1), the *fms*-like tyrosine kinase receptor Flt-1 and the *fms*-like tyrosine kinase receptor Flt-4. Two of these related RTKs, namely Flt-1 and KDR, have been shown to bind VEGF with high affinity.

Accordingly, antagonism of the activity of VEGF is expected to be beneficial in the  
5 treatment of a number of disease states that are associated with angiogenesis and/or increased vascular permeability such as cancer, especially in inhibiting the development of tumours.

It is disclosed in International Patent Application WO 00/21955 that certain  
4-(3-pyrazolyloxy)- and 4-(3-pyrazolylamino)- quinazoline derivatives possess antiangiogenic  
and/or vascular permeability reducing activity based on antagonism of the activity of VEGF.  
10 There is no mention therein of 4-(4-pyrazolyloxy)quinoline derivatives.

It is known that several compounds with PDGF receptor kinase inhibitory activity are  
progressing toward clinical development. The 2-anilinopyrimidine derivative known as  
imatinib (STI571; Nature Reviews, 2002, 1, 493-502; Cancer Research, 1996, 56, 100-104) has  
been shown to inhibit PDGF receptor kinase activity although its current clinical use is for the  
15 treatment of CML based on its additional activity as an inhibitor of BCR-ABL kinase. STI571  
inhibits the growth of glioblastoma tumours arising from injection into the brains of nude mice  
of the human glioblastoma lines U343 and U87 (Cancer Research, 2000, 60, 5143-5150). The  
compound also inhibits the *in vivo* growth of dermatofibrosarcoma protruberans cell cultures  
(Cancer Research, 2001, 61, 5778-5783). Based on the PDGF receptor kinase inhibitory activity  
20 of the compound, clinical trials are being carried out in glioblastoma and in prostate cancer.  
Several other PDGF receptor kinase inhibitors are being investigated including quinoline,  
quinazoline and quinoxaline derivatives (Cytokine & Growth Factor Reviews, 2004, 15, 229-  
235).

It is further known from International Patent Application WO 92/20642 that certain aryl  
25 and heteroaryl compounds inhibit EGF and/or PDGF receptor tyrosine kinase. There is the  
disclosure of certain quinazoline derivatives therein but no mention is made of  
4-(4-pyrazolyloxy)quinoline derivatives.

It is stated in US Patent No. 5,476,851 that certain pyrazolo[3,4-g]quinoxaline  
derivatives possess PDGF receptor kinase inhibitory activity.

30 It is stated in International Patent Application WO 01/40217 that certain  
*N*-(2-quinolyl)benzimidazole derivatives are selective inhibitors of PDGF receptor kinase that  
are useful in the treatment of cell proliferation disorders.

- 5 -

It is stated in International Patent Application WO 02/12242 that certain bicyclic pyrazole derivatives are useful for treating diseases linked to dysregulated protein kinases and in International Patent Application WO 03/097609 that certain tricyclic 3-aminopyrazole derivatives possess PDGF receptor kinase inhibitory activity.

5 It is disclosed in many published patent applications that 4-anilinoquinolines and 4-aryloxyquinolines possess tyrosine kinase enzyme inhibitory activity. However, there is no specific mention therein of 4-(4-pyrazolyloxy)quinoline derivatives; in particular, there is no specific mention made therein of such compounds that bear an acetamido substituent on the pyrazole ring.

10 As stated above, although STI571 is the only compound with PDGF receptor kinase inhibitory activity that appears to have yet reached the market, that compound possesses approximately equipotent activity against various other kinase enzymes. There is still a need for further compounds with PDGF receptor kinase inhibitory activity that may be useful for the treatment of cell proliferation disorders such as cancer.

15 We have now found that surprisingly certain novel 4-(4-pyrazolyloxy)quinoline derivatives that bear an acetamido substituent on the pyrazole ring possess potent activity against cell proliferative disorders. It is believed that the compounds provide a useful treatment of cell proliferative disorders, for example to provide an anti-tumour effect, by way of a contribution from inhibition of PDGF receptor tyrosine kinases.

20 A further characteristic of hyperproliferative diseases such as cancer is damage to the cellular pathways that control progress through the cell cycle which, in normal eukaryotic cells, involves an ordered cascade of protein phosphorylation. As for signal transduction mechanisms, several families of protein kinases appear to play critical roles in the cell cycle cascade. The most widely studied of these cell cycle regulators is the cyclin dependent kinase  
25 family (the CDKs). Activity of specific CDKs at specific times is essential both to initiate and coordinate progress through the cell cycle. For example, the CDK4 protein appears to control entry into the cell cycle (the G0-G1-S transition) by phosphorylating the retinoblastoma gene product pRb which stimulates the release of the transcription factor E2F from pRb which, in turn, acts to increase the transcription of genes necessary for entry into S phase. The catalytic  
30 activity of CDK4 is stimulated by binding to a partner protein, Cyclin D. One of the first demonstrations of a direct link between cancer and the cell cycle was made with the observation that the Cyclin D1 gene was amplified and Cyclin D protein levels increased in many human tumours.

- 6 -

More recently, protein kinases that are structurally distinct from the CDK family have been identified which play critical roles in regulating the cell cycle and which also appear to be important in oncogenesis. They include the human homologues of the *Drosophila* aurora and *S.cerevisiae* Ipl1 proteins. The three human homologues of these genes Aurora-A, Aurora-B and Aurora-C encode cell cycle regulated serine-threonine protein kinases that show a peak of expression and kinase activity through G2 and mitosis. Several observations implicate the involvement of human aurora proteins in cancer, especially Aurora-A and Aurora-B. Abrogation of Aurora-A expression and function by antisense oligonucleotide treatment of human tumour cell lines leads to cell cycle arrest and exerts an anti-proliferative effect. Additionally, small molecule inhibitors of Aurora-A and Aurora-B have been demonstrated to have an anti-proliferative effect in human tumour cells.

It is disclosed in International Patent Application WO 02/00649 that certain quinazoline derivatives that carry a 5-membered heteroaryl group linked to the 4-position of the quinazoline ring by a NH group possess Aurora kinase inhibitory activity. There is no mention therein of 4-(4-pyrazolyloxy)quinoline derivatives.

It is disclosed in International Patent Application WO 03/055491 and WO 04/058781 that certain 4-(3-pyrazolylamino)quinazoline derivatives possess Aurora kinase inhibitory activity. There is no mention therein of 4-(4-pyrazolyloxy)quinoline derivatives.

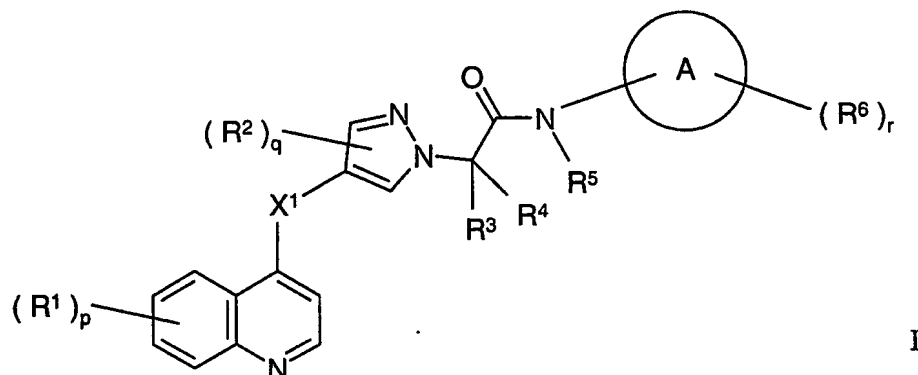
It is stated in International Patent Application PCT/GB2004/001614 (published subsequently as WO 2004/094410) that certain 4-(4-pyrazolylamino)quinazoline derivatives possess Aurora kinase inhibitory activity. There is no disclosure therein of 4-(4-pyrazolyloxy)quinoline derivatives.

As stated above, we have now found that surprisingly certain novel 4-(4-pyrazolyloxy)quinoline derivatives that bear an acetamido substituent on the pyrazole ring possess potent activity against cell proliferative disorders. Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on one or two biological processes, it is believed that the compounds provide a useful treatment of cell proliferative disorders, for example to provide an anti-tumour effect, by way of a contribution from inhibition of PDGF receptor tyrosine kinases. In particular, it is believed that the compounds of the present invention provide a useful treatment of cell proliferative disorders by way of a contribution from inhibition of the PDGF $\alpha$  and/or PDGF $\beta$  receptor tyrosine kinases.

- 7 -

Generally the compounds of the present invention possess potent inhibitory activity against the PDGF receptor family of tyrosine kinases, for example the PDGF $\alpha$  and/or PDGF $\beta$  receptor tyrosine kinases whilst possessing less potent inhibitory activity against other tyrosine kinase enzymes such as the EGF receptor tyrosine kinase and VEGF receptor tyrosine kinases such as KDR and Flt-1. Furthermore, certain compounds of the present invention possess substantially better potency against the PDGF receptor family of tyrosine kinases, particularly against the PDGF $\beta$  receptor tyrosine kinase than against EGF receptor tyrosine kinase or VEGF receptor tyrosine kinases such as KDR. Such compounds possess sufficient potency that they may be used in an amount sufficient to inhibit the PDGF receptor family of tyrosine kinases, particularly PDGF $\beta$  receptor tyrosine kinase whilst demonstrating little activity against EGF receptor tyrosine kinase or against VEGF receptor tyrosine kinases such as KDR.

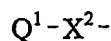
According to one aspect of the invention there is provided a quinoline derivative of the Formula I



wherein X<sup>1</sup> is O or N(R<sup>7</sup>) where R<sup>7</sup> is hydrogen or (1-8C)alkyl;

p is 0, 1, 2 or 3;

each R<sup>1</sup> group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, hydroxy, mercapto, amino, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or from a group of the formula :



wherein X<sup>2</sup> is a direct bond or is selected from O, S, SO, SO<sub>2</sub>, N(R<sup>8</sup>), CO, CON(R<sup>8</sup>), N(R<sup>8</sup>)CO, OC(R<sup>8</sup>)<sub>2</sub> and N(R<sup>8</sup>)C(R<sup>8</sup>)<sub>2</sub>, wherein each R<sup>8</sup> is hydrogen or (1-8C)alkyl, and Q<sup>1</sup> is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl,



- 8 -

(3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocyclyl group within a R<sup>1</sup> substituent optionally bears 1, 2 or 3 substituents, which may be the same or  
 5 different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-6C)alkyl]carbamoyl,  
 10 (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylureido, *N'*-(1-6C)alkylureido, *N',N'*-di-[(1-6C)alkyl]ureido, *N,N'*-di-[(1-6C)alkyl]ureido, *N,N',N'*-tri-[(1-6C)alkyl]ureido, *N*-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

15  $-X^3-R^9$

wherein X<sup>3</sup> is a direct bond or is selected from O and N(R<sup>10</sup>), wherein R<sup>10</sup> is hydrogen or (1-8C)alkyl, and R<sup>9</sup> is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, mercapto-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, (1-6C)alkylsulphinyl-(1-6C)alkyl, (1-6C)alkylsulphonyl-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl,  
 20 (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, *N*-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl, ureido-(1-6C)alkyl, *N*-(1-6C)alkylureido-(1-6C)alkyl, *N'*-(1-6C)alkylureido-(1-6C)alkyl, *N',N'*-di-[(1-6C)alkyl]ureido-(1-6C)alkyl, *N,N'*-di-[(1-6C)alkyl]ureido-(1-6C)alkyl or *N,N',N'*-tri-[(1-6C)alkyl]ureido-(1-6C)alkyl, or  
 25 from a group of the formula :

$-X^4-Q^2$

wherein X<sup>4</sup> is a direct bond or is selected from O, CO and N(R<sup>11</sup>), wherein R<sup>11</sup> is hydrogen or (1-8C)alkyl, and Q<sup>2</sup> is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or  
 30 different, selected from halogeno, hydroxy, (1-8C)alkyl and (1-6C)alkoxy,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R<sup>1</sup> optionally bears a (1-3C)alkylenedioxy group,

- 9 -

and wherein any heterocyclyl group within a  $R^1$  substituent optionally bears 1 or 2 oxo or thioxo substituents,

and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a  $R^1$  substituent optionally bears on each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more halogeno or (1-8C)alkyl substituents and/or a  
 5 substituent selected from hydroxy, mercapto, amino, cyano, carboxy, carbamoyl, ureido, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylureido, *N'*-(1-6C)alkylureido,  
 10 *N',N'*-di-[(1-6C)alkyl]ureido, *N,N'*-di-[(1-6C)alkyl]ureido, *N,N',N'*-tri-[(1-6C)alkyl]ureido, *N*-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a  $R^1$  substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO<sub>2</sub>,  
 15  $N(R^{12})$ , CO, CH(OR<sup>12</sup>), CON(R<sup>12</sup>),  $N(R^{12})CO$ ,  $N(R^{12})CON(R^{12})$ , SO<sub>2</sub> $N(R^{12})$ ,  $N(R^{12})SO_2$ , CH=CH and C≡C wherein  $R^{12}$  is hydrogen or (1-8C)alkyl, or, when the inserted group is  $N(R^{12})$ ,  $R^{12}$  may also be (2-6C)alkanoyl;

$q$  is 0, 1 or 2;

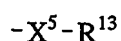
each  $R^2$  group, which may be the same or different, is selected from halogeno,  
 20 trifluoromethyl, cyano, hydroxy, amino, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

$R^3$  is hydrogen, (1-8C)alkyl, (2-8C)alkenyl or (2-8C)alkynyl;

$R^4$  is hydrogen, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl,  
 25 amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, *N*-(1-6C)alkylcarbamoyl-(1-6C)alkyl, *N,N*-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or *N*-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl;

or  $R^3$  and  $R^4$  together with the carbon atom to which they are attached form a  
 30 (3-8C)cycloalkyl group;

$R^5$  is hydrogen, (1-8C)alkyl, (2-8C)alkenyl or (2-8C)alkynyl or a group of the formula :



- 10 -

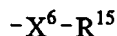
wherein  $X^5$  is a direct bond or is selected from O and  $N(R^{14})$ , wherein  $R^{14}$  is hydrogen or (1-8C)alkyl, and  $R^{13}$  is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl or cyano-(1-6C)alkyl;

**Ring A** is a 6-membered monocyclic or a 10-membered bicyclic aryl ring or a

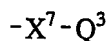
- 5 5- or 6-membered monocyclic or a 9- or 10-membered bicyclic heteroaryl ring with up to three ring heteroatoms selected from oxygen, nitrogen and sulphur;

**r** is 0, 1, 2 or 3; and

- each  $R^6$  group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, hydroxy, mercapto, amino, carboxy, carbamoyl, sulphamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N'*-(1-6C)alkylureido, *N',N'*-di-[(1-6C)alkyl]ureido, *N*-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



- wherein  $X^6$  is a direct bond or is selected from O and  $N(R^{16})$ , wherein  $R^{16}$  is hydrogen or (1-8C)alkyl, and  $R^{15}$  is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, mercapto-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, (1-6C)alkylsulphinyl-(1-6C)alkyl, (1-6C)alkylsulphonyl-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, *N*-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, *N*-(1-6C)alkylcarbamoyl-(1-6C)alkyl, *N,N*-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, sulphamoyl-(1-6C)alkyl, *N*-(1-6C)alkylsulphamoyl-(1-6C)alkyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl-(1-6C)alkyl, ureido-(1-6C)alkyl, *N*-(1-6C)alkylureido-(1-6C)alkyl, *N'*-(1-6C)alkylureido-(1-6C)alkyl, *N',N'*-di-[(1-6C)alkyl]ureido-(1-6C)alkyl, *N,N'*-di-[(1-6C)alkyl]ureido-(1-6C)alkyl, *N,N',N'*-tri-[(1-6C)alkyl]ureido-(1-6C)alkyl, (1-6C)alkanesulphonylamino-(1-6C)alkyl or *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino-(1-6C)alkyl, or from a group of the formula :



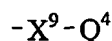
## - 11 -

wherein  $X^7$  is a direct bond or is selected from O, S, SO, SO<sub>2</sub>, N(R<sup>17</sup>), CO, CH(OR<sup>17</sup>), CON(R<sup>17</sup>), N(R<sup>17</sup>)CO, N(R<sup>17</sup>)CON(R<sup>17</sup>), SO<sub>2</sub>N(R<sup>17</sup>), N(R<sup>17</sup>)SO<sub>2</sub>, C(R<sup>17</sup>)<sub>2</sub>O, C(R<sup>17</sup>)<sub>2</sub>S and C(R<sup>17</sup>)<sub>2</sub>N(R<sup>17</sup>), wherein each R<sup>17</sup> is hydrogen or (1-8C)alkyl, and Q<sup>3</sup> is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl, (3-8C)cycloalkenyl-  
 5 (1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or two R<sup>6</sup> groups together form a bivalent group that spans adjacent ring positions on Ring A selected from OC(R<sup>18</sup>)<sub>2</sub>O, OC(R<sup>18</sup>)<sub>2</sub>C(R<sup>18</sup>)<sub>2</sub>O, OC(R<sup>18</sup>)<sub>2</sub>C(R<sup>18</sup>)<sub>2</sub>, C(R<sup>18</sup>)<sub>2</sub>OC(R<sup>18</sup>)<sub>2</sub>, OC(R<sup>18</sup>)<sub>2</sub>N(R<sup>19</sup>), N(R<sup>19</sup>)C(R<sup>18</sup>)<sub>2</sub>N(R<sup>19</sup>), N(R<sup>19</sup>)C(R<sup>18</sup>)<sub>2</sub>C(R<sup>18</sup>)<sub>2</sub>, C(R<sup>18</sup>)<sub>2</sub>N(R<sup>19</sup>)C(R<sup>18</sup>)<sub>2</sub>, CO.N(R<sup>18</sup>)C(R<sup>18</sup>)<sub>2</sub>, N(R<sup>18</sup>)CO.C(R<sup>18</sup>)<sub>2</sub>, N(R<sup>19</sup>)C(R<sup>18</sup>)<sub>2</sub>CO, CO.N(R<sup>18</sup>)CO, N(R<sup>19</sup>)N(R<sup>18</sup>)CO,  
 10 N(R<sup>18</sup>)CO.N(R<sup>18</sup>), O.CO.N(R<sup>18</sup>), O.CO.C(R<sup>18</sup>)<sub>2</sub> and CO.OC(R<sup>18</sup>)<sub>2</sub> wherein each R<sup>18</sup> is hydrogen, (1-8C)alkyl, (2-8C)alkenyl or (2-8C)alkynyl, and wherein R<sup>19</sup> is hydrogen, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl or (2-6C)alkanoyl, and wherein any aryl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocyclyl group within an R<sup>6</sup> group optionally bears 1, 2 or 3 substituents, which may be the same or  
 15 different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-6C)alkyl]carbamoyl,  
 20 (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N'*-(1-6C)alkylureido, *N',N'*-di-[(1-6C)alkyl]ureido, *N*-(1-6C)alkylureido, *N,N'*-di-[(1-6C)alkyl]ureido, *N,N',N'*-tri-[(1-6C)alkyl]ureido, *N*-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

25  $-X^8-R^{20}$

wherein  $X^8$  is a direct bond or is selected from O and N(R<sup>21</sup>), wherein R<sup>21</sup> is hydrogen or (1-8C)alkyl, and R<sup>20</sup> is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, mercapto-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, (1-6C)alkylsulphinyl-(1-6C)alkyl, (1-6C)alkylsulphonyl-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl,  
 30 (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or *N*-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl, or from a group of the formula :

- 12 -



wherein  $X^9$  is a direct bond or is selected from O, CO and  $N(R^{22})$ , wherein  $R^{22}$  is hydrogen or (1-8C)alkyl, and  $Q^4$  is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or  
 5 different, selected from halogeno, hydroxy, (1-8C)alkyl and (1-6C)alkoxy,

and wherein any aryl, heteroaryl or heterocyclyl group within an  $R^6$  group optionally bears a (1-3C)alkylenedioxy group,

and wherein any heterocyclyl group within an  $R^6$  group optionally bears 1 or 2 oxo or thioxo substituents,

10 and wherein any CH,  $CH_2$  or  $CH_3$  group within an  $R^6$  group optionally bears on each said CH,  $CH_2$  or  $CH_3$  group one or more halogeno or (1-8C)alkyl substituents and/or a substituent selected from hydroxy, mercapto, amino, cyano, carboxy, carbamoyl, ureido, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl,  
 15 *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N'*-(1-6C)alkylureido, *N',N'*-di-[(1-6C)alkyl]ureido, *N*-(1-6C)alkylureido, *N,N'*-di-[(1-6C)alkyl]ureido, *N,N',N'*-tri-[(1-6C)alkyl]ureido, *N*-(1-6C)alkylsulphamoyl, *N*-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-  
 20 (1-6C)alkanesulphonylamino,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within an  $R^6$  group are optionally separated by the insertion into the chain of a group selected from O, S, SO,  $SO_2$ ,  $N(R^{23})$ ,  $N(R^{23})CO$ ,  $CON(R^{23})$ ,  $N(R^{23})CON(R^{23})$ , CO,  $CH(OR^{23})$ ,  $N(R^{23})SO_2$ ,  $SO_2N(R^{23})$ ,  $CH=CH$  and  $C\equiv C$  wherein  $R^{23}$  is hydrogen or (1-8C)alkyl, or, when the inserted group is  
 25  $N(R^{23})$ ,  $R^{23}$  may also be (2-6C)alkanoyl;  
 or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

In this specification the generic term "(1-8C)alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and *tert*-butyl, and also (3-8C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and  
 30 cycloheptyl, and also (3-6C)cycloalkyl-(1-2C)alkyl groups such as cyclopropylmethyl, 2-cyclopropylethyl, cyclobutylmethyl, 2-cyclobutylethyl, cyclopentylmethyl, 2-cyclopentylethyl, cyclohexylmethyl and 2-cyclohexylethyl. However references to individual

- 13 -

alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes (3-6C)cycloalkyloxy groups and (3-5C)cycloalkyl-(1-2C)alkoxy groups, for example methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cyclopropylmethoxy, 2-cyclopropylethoxy, cyclobutylmethoxy, 2-cyclobutylethoxy and cyclopentylmethoxy; (1-6C)alkylamino includes (3-6C)cycloalkylamino groups and (3-5C)cycloalkyl-(1-2C)alkylamino groups, for example methylamino, ethylamino, propylamino, cyclopropylamino, cyclobutylamino, cyclohexylamino, cyclopropylmethylamino, 2-cyclopropylethylamino, cyclobutylmethylamino, 2-cyclobutylethylamino and cyclopentylmethylamino; and di-[(1-6C)alkyl]amino includes di-[(3-6C)cycloalkyl]amino groups and di-[(3-5C)cycloalkyl-(1-2C)alkyl]amino groups, for example dimethylamino, diethylamino, dipropylamino, *N*-cyclopropyl-*N*-methylamino, *N*-cyclobutyl-*N*-methylamino, *N*-cyclohexyl-*N*-ethylamino, *N*-cyclopropylmethyl-*N*-methylamino, *N*-(2-cyclopropylethyl)-*N*-methylamino and *N*-cyclopentylmethyl-*N*-methylamino.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

It is to be understood that certain compounds of Formula I defined above may exhibit the phenomenon of tautomerism. In particular, tautomerism may affect heteroaryl rings within the definition of Ring A or heterocyclic groups within the  $R^1$  and  $R^6$  groups that bear 1 or 2 oxo or thioxo substituents. It is to be understood that the present invention includes in its definition any such tautomeric form, or a mixture thereof, which possesses the above-mentioned activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings or named in the Examples.

- 14 -

In structural Formula I, it is to be understood that there is a hydrogen atom at the 2-position on the quinoline ring. It is to be understood thereby that the R<sup>1</sup> substituents may only be located at the 3-, 5-, 6-, 7- or 8-positions on the quinoline ring *i.e.* that the 2-position remains unsubstituted. Conveniently, the 3-position on the quinoline ring also remains  
5 unsubstituted or the R<sup>1</sup> substituent at the 3-position on the quinoline ring is a cyano group. Conveniently, other R<sup>1</sup> substituents may only be located at the 5-, 6- or 7-positions on the quinoline ring.

In structural Formula I, it is further to be understood that any R<sup>2</sup> group that may be present on the pyrazolyl group may be located at any available position. Conveniently, there is  
10 a single R<sup>2</sup> group. More conveniently, no R<sup>2</sup> group is present (q=0).

In structural Formula I, it is to be understood that any R<sup>6</sup> group may be located at any available position on Ring A. For example, an R<sup>6</sup> group may be located at the 3- or 4-position (relative to the CON(R<sup>5</sup>) group) when Ring A is a 6-membered ring or, for example, it may be located at the 3-position (relative to the CON(R<sup>5</sup>) group) when Ring A is a  
15 5-membered ring.

Suitable values for the generic radicals referred to above include those set out below.

A suitable value for any one of the 'Q' groups (Q<sup>1</sup> to Q<sup>4</sup>) within the R<sup>1</sup> or R<sup>6</sup> groups when the 'Q' group is aryl or for the aryl group within any 'Q' group is, for example, phenyl or naphthyl, preferably phenyl.

20 A suitable value for any one of the 'Q' groups (Q<sup>1</sup> or Q<sup>3</sup>) within the R<sup>1</sup> or R<sup>6</sup> groups when the 'Q' group is (3-8C)cycloalkyl or for the (3-8C)cycloalkyl group within any 'Q' group is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl or cyclooctyl.

A suitable value for the (3-8C)cycloalkyl group formed when R<sup>3</sup> and R<sup>4</sup> together with  
25 the carbon atom to which they are attached form a (3-8C)cycloalkyl group is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

A suitable value for any one of the 'Q' groups (Q<sup>1</sup> or Q<sup>3</sup>) within the R<sup>1</sup> or R<sup>6</sup> groups when the 'Q' group is (3-8C)cycloalkenyl or for the (3-8C)cycloalkenyl group within any 'Q' group is, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl or  
30 cyclooctenyl.

A suitable value for any one of the 'Q' groups (Q<sup>1</sup> to Q<sup>4</sup>) within the R<sup>1</sup> or R<sup>6</sup> groups when the 'Q' group is heteroaryl or for the heteroaryl group within any 'Q' group is, for example, an aromatic 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring

with up to five ring heteroatoms selected from oxygen, nitrogen and sulphur, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, 5 benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxaliny, cinnoliny or naphthyridinyl.

A suitable value for any one of the 'Q' groups ( $Q^1$  to  $Q^4$ ) within the  $R^1$  or  $R^6$  groups when the 'Q' group is heterocyclyl or for the heterocyclyl group within any 'Q' group is, for example, a non-aromatic saturated or partially saturated 3 to 10 membered monocyclic or 10 bicyclic ring with up to five heteroatoms selected from oxygen, nitrogen and sulphur, for example oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepanyl, tetrahydrothienyl, 1,1-dioxotetrahydrothienyl, tetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, aziridinyl, azetidiny, pyrrolinyl, pyrrolidinyl, imidazoliny, imidazolidiny, pyrazoliny, pyrazolidiny, morpholiny, tetrahydro-1,4-thiaziny, 1,1-dioxotetrahydro-1,4-thiaziny, piperidinyl, 15 homopiperidinyl, piperaziny, homopiperaziny, 2-azabicyclo[2.2.1]heptyl, quinuclidiny, chromanyl, isochromanyl, indoliny, isoindoliny, dihydropyridiny, tetrahydropyridiny, dihydropyrimidinyl or tetrahydropyrimidinyl, preferably tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrroliny, pyrrolidinyl, morpholiny, piperidinyl, piperaziny, indoliny or isoindoliny. A suitable value for such a group which bears 1 or 2 oxo or thioxo substituents 20 is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidiny, 2-thioxoimidazolidiny, 2-oxopiperidinyl, 4-oxo-1,4-dihydropyridiny, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidiny or 2,6-dioxopiperidinyl.

A suitable value for any 'Q' group when it is heteroaryl-(1-6C)alkyl is, for example, heteroarylmethyl, 2-heteroarylethyl and 3-heteroarylpropyl. The invention comprises 25 corresponding suitable values for 'Q' groups when, for example, rather than a heteroaryl-(1-6C)alkyl group, an aryl-(1-6C)alkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group is present.

A suitable value for Ring A when it is a 6-membered monocyclic or a 10-membered bicyclic aryl ring or a 5- or 6-membered monocyclic or a 9- or 10-membered bicyclic 30 heteroaryl ring with up to three ring heteroatoms selected from oxygen, nitrogen and sulphur is, for example, phenyl, naphthyl, furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl,



- 16 -

benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl. Conveniently, Ring A is a phenyl, furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl ring. More conveniently, Ring A is a phenyl, pyridyl, pyrimidinyl, pyrazinyl or  
 5 pyridazinyl ring.

Suitable values for any of the 'R' groups ( $R^1$  to  $R^{23}$ ), or for various groups within an  $R^1$ ,  $R^2$  or  $R^6$  substituent include :-

- |  |  |
|--|--|
| for halogeno                                   | fluoro, chloro, bromo and iodo;  |
| for (1-8C)alkyl:                               | methyl, ethyl, propyl, isopropyl, <i>tert</i> -butyl,  |
| 10   | cyclobutyl, cyclohexyl, cyclohexylmethyl and 2-cyclopropylethyl;   |
| for (2-8C)alkenyl:                             | vinyl, isopropenyl, allyl and but-2-enyl;  |
| for (2-8C)alkynyl:                             | ethynyl, 2-propynyl and but-2-ynyl;  |
| for (1-6C)alkoxy:                              | methoxy, ethoxy, propoxy, isopropoxy and butoxy;   |
| 15   | for (2-6C)alkenyloxy: vinyloxy and allyloxy;   |
| for (2-6C)alkynyloxy:                          | ethynyloxy and 2-propynyloxy;  |
| for (1-6C)alkylthio:                           | methylthio, ethylthio and propylthio;  |
| for (1-6C)alkylsulphinyl:                      | methylsulphinyl and ethylsulphinyl;  |
| for (1-6C)alkylsulphonyl:                      | methylsulphonyl and ethylsulphonyl;  |
| 20   | for (1-6C)alkylamino: methylamino, ethylamino, propylamino, isopropylamino and butylamino;                             |
| for di-[(1-6C)alkyl]amino:                     | dimethylamino, diethylamino, <i>N</i> -ethyl- <i>N</i> -methylamino and diisopropylamino;                              |
| for (1-6C)alkoxycarbonyl:                      | methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and <i>tert</i> -butoxycarbonyl;                                      |
| 25   | for <i>N</i> -(1-6C)alkylcarbamoyl: <i>N</i> -methylcarbamoyl, <i>N</i> -ethylcarbamoyl and <i>N</i> -propylcarbamoyl; |
| for <i>N,N</i> -di-[(1-6C)alkyl]carbamoyl:     | <i>N,N</i> -dimethylcarbamoyl, <i>N</i> -ethyl- <i>N</i> -methylcarbamoyl and <i>N,N</i> -diethylcarbamoyl;            |
| 30   | for (2-6C)alkanoyl: acetyl, propionyl and isobutyryl;  |
| for (2-6C)alkanoyloxy:                         | acetoxyl and propionyloxy;   |
| for (2-6C)alkanoylamino:                       | acetamido and propionamido;  |
| for <i>N</i> -(1-6C)alkyl-(2-6C)alkanoylamino: | <i>N</i> -methylacetamido and <i>N</i> -methylpropionamido;  |

- 17 -

- for *N'*-(1-6C)alkylureido: *N'*-methylureido and *N'*-ethylureido;
- for *N',N'*-di-[(1-6C)alkyl]ureido: *N',N'*-dimethylureido and *N'*-methyl-*N'*-ethylureido;
- for *N*-(1-6C)alkylureido: *N*-methylureido and *N*-ethylureido;
- for *N,N'*-di-[(1-6C)alkyl]ureido: *N,N'*-dimethylureido, *N*-methyl-*N'*-ethylureido and
- 5 *N*-ethyl-*N'*-methylureido;
- for *N,N',N'*-di-[(1-6C)alkyl]ureido: *N,N',N'*-trimethylureido,
- N*-ethyl-*N',N'*-dimethylureido and
- N*-methyl-*N',N'*-diethylureido;
- for *N*-(1-6C)alkylsulphamoyl: *N*-methylsulphamoyl and *N*-ethylsulphamoyl;
- 10 for *N,N*-di-[(1-6C)alkyl]sulphamoyl: *N,N*-dimethylsulphamoyl;
- for (1-6C)alkanesulphonylamino: methanesulphonylamino and ethanesulphonylamino;
- for *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino: *N*-methylmethanesulphonylamino and
- N*-methylethanesulphonylamino;
- for halogeno-(1-6C)alkyl: chloromethyl, 2-fluoroethyl, 2-chloroethyl,
- 15 1-chloroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl,
- 3-fluoropropyl, 3-chloropropyl, 3,3-difluoropropyl
- and 3,3,3-trifluoropropyl;
- for hydroxy-(1-6C)alkyl: hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and
- 3-hydroxypropyl;
- 20 for mercapto-(1-6C)alkyl: mercaptomethyl, 2-mercaptoethyl, 1-mercaptoethyl
- and 3-mercaptopropyl;
- for (1-6C)alkoxy-(1-6C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxyethyl,
- 2-methoxyethyl, 2-ethoxyethyl and
- 3-methoxypropyl;
- 25 for (1-6C)alkylthio-(1-6C)alkyl: methylthiomethyl, ethylthiomethyl,
- 2-methylthioethyl, 1-methylthioethyl and
- 3-methylthiopropyl;
- for (1-6C)alkylsulphinyl-(1-6C)alkyl: methylsulphinylmethyl, ethylsulphinylmethyl,
- 2-methylsulphinylethyl, 1-methylsulphinylethyl and
- 3-methylsulphinylpropyl;
- 30 for (1-6C)alkylsulphonyl-(1-6C)alkyl: methylsulphonylmethyl, ethylsulphonylmethyl,
- 2-methylsulphonylethyl, 1-methylsulphonylethyl and
- 3-methylsulphonylpropyl;

## - 18 -

- for cyano-(1-6C)alkyl: cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and 3-cyanopropyl;
- for amino-(1-6C)alkyl: aminomethyl, 2-aminoethyl, 1-aminoethyl, 3-aminopropyl, 1-aminopropyl and 5-aminopropyl;
- 5 for (1-6C)alkylamino-(1-6C)alkyl: methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl and 3-methylaminopropyl;
- for di-[(1-6C)alkyl]amino-(1-6C)alkyl: dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl;
- 10 for (2-6C)alkanoylamino-(1-6C)alkyl: acetamidomethyl, propionamidomethyl, 2-acetamidoethyl and 1-acetamidoethyl;
- for *N*-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl:
- 15 *N*-methylacetamidomethyl, *N*-methylpropionamidomethyl, 2-(*N*-methylacetamido)ethyl and 1-(*N*-methylacetamido)ethyl;
- for (1-6C)alkoxycarbonylamino-(1-6C)alkyl: methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl, 20 *tert*-butoxycarbonylaminomethyl and 2-methoxycarbonylaminoethyl.
- for ureido-(1-6C)alkyl: ureidomethyl, 2-ureidoethyl and 1-ureidoethyl;
- for *N'*-(1-6C)alkylureido-(1-6C)alkyl: *N'*-methylureidomethyl, 2-(*N'*-methylureido)ethyl and 1-(*N'*-methylureido)ethyl;
- 25 for *N',N'*-di-[(1-6C)alkyl]ureido-(1-6C)alkyl: *N',N'*-dimethylureidomethyl, 2-(*N',N'*-dimethylureido)ethyl and 1-(*N',N'*-dimethylureido)ethyl;
- for *N*-(1-6C)alkylureido-(1-6C)alkyl: *N*-methylureidomethyl, 2-(*N*-methylureido)ethyl and 1-(*N*-methylureido)ethyl;
- 30 for *N,N'*-di-[(1-6C)alkyl]ureido-(1-6C)alkyl: *N,N'*-dimethylureidomethyl, 2-(*N,N'*-dimethylureido)ethyl and 1-(*N,N'*-dimethylureido)ethyl;

## - 19 -

- for *N,N,N'*-di-[(1-6C)alkyl]ureido-(1-6C)alkyl: *N,N,N'*-trimethylureidomethyl,  
2-(*N,N,N'*-trimethylureido)ethyl and  
1-(*N,N,N'*-trimethylureido)ethyl;
- for carboxy-(1-6C)alkyl: carboxymethyl, 1-carboxyethyl, 2-carboxyethyl,  
5 3-carboxypropyl and 4-carboxybutyl;
- for (1-6C)alkoxycarbonyl-(1-6C)alkyl: methoxycarbonylmethyl, ethoxycarbonylmethyl,  
*tert*-butoxycarbonylmethyl, 1-methoxycarbonylethyl,  
1-ethoxycarbonylethyl, 2-methoxycarbonylethyl,  
2-ethoxycarbonylethyl, 3-methoxycarbonylpropyl and  
10 3-ethoxycarbonylpropyl;
- for carbamoyl-(1-6C)alkyl: carbamoylmethyl, 1-carbamoylethyl,  
2-carbamoylethyl and 3-carbamoylpropyl;
- for *N*-(1-6C)alkylcarbamoyl-(1-6C)alkyl: *N*-methylcarbamoylmethyl, *N*-ethylcarbamoylmethyl,  
*N*-propylcarbamoylmethyl,  
15 1-(*N*-methylcarbamoyl)ethyl,  
1-(*N*-ethylcarbamoyl)ethyl,  
2-(*N*-methylcarbamoyl)ethyl,  
2-(*N*-ethylcarbamoyl)ethyl and  
3-(*N*-methylcarbamoyl)propyl;
- 20 for *N,N*-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl: *N,N*-dimethylcarbamoylmethyl,  
*N*-ethyl-*N*-methylcarbamoylmethyl,  
*N,N*-diethylcarbamoylmethyl,  
1-(*N,N*-dimethylcarbamoyl)ethyl,  
1-(*N,N*-diethylcarbamoyl)ethyl,  
25 2-(*N,N*-dimethylcarbamoyl)ethyl,  
2-(*N,N*-diethylcarbamoyl)ethyl,  
3-(*N,N*-dimethylcarbamoyl)propyl and  
4-(*N,N*-dimethylcarbamoyl)butyl;
- for sulphamoyl-(1-6C)alkyl: sulphamoylmethyl, 1-sulphamoylethyl,  
30 2-sulphamoylethyl and 3-sulphamoylpropyl;
- for *N*-(1-6C)alkylsulphamoyl-(1-6C)alkyl: *N*-methylsulphamoylmethyl,  
1-(*N*-methylsulphamoyl)ethyl,

- 20 -

2-(*N*-methylsulphamoyl)ethyl, and

3-(*N*-methylsulphamoyl)propyl;

for *N,N*-di-[(1-6C)alkyl]sulphamoyl-(1-6C)alkyl: *N,N*-dimethylsulphamoylmethyl,

1-(*N,N*-dimethylsulphamoyl)ethyl,

5 2-(*N,N*-dimethylsulphamoyl)ethyl and

3-(*N,N*-dimethylsulphamoyl)propyl;

for (1-6C)alkanesulphonylamino-(1-6C)alkyl: methanesulphonylaminomethyl,

2-(methanesulphonylamino)ethyl and

1-(methanesulphonylamino)ethyl; and

10 for *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino-(1-6C)alkyl:

*N*-methylmethanesulphonylaminomethyl,

2-(*N*-methylmethanesulphonylamino)ethyl and

1-(*N*-methylmethanesulphonylamino)ethyl.

A suitable value for a (1-3C)alkylenedioxy group that may be present within a R<sup>1</sup> or R<sup>6</sup>  
15 group is, for example, methylenedioxy, ethylenedioxy, isopropylidenedioxy or ethylenedioxy  
and the oxygen atoms thereof occupy adjacent ring positions.

When, as defined hereinbefore, an R<sup>1</sup> group forms a group of the formula Q<sup>1</sup>-X<sup>2</sup>- and,  
for example, X<sup>2</sup> is a OC(R<sup>8</sup>)<sub>2</sub> linking group, it is the carbon atom, not the oxygen atom, of the  
OC(R<sup>8</sup>)<sub>2</sub> linking group which is attached to the quinoline ring and the oxygen atom is attached  
20 to the Q<sup>1</sup> group. Similarly, when, as defined hereinbefore, an R<sup>6</sup> group forms a group of the  
formula -X<sup>7</sup>-Q<sup>3</sup> and, for example, X<sup>7</sup> is a C(R<sup>17</sup>)<sub>2</sub>O linking group, it is the oxygen atom of the  
C(R<sup>17</sup>)<sub>2</sub>O linking group which is attached to the Q<sup>3</sup> group.

A suitable (2-6C)alkylene chain within a R<sup>1</sup> or R<sup>6</sup> group is, for example, an ethylene,  
trimethylene, tetramethylene or pentamethylene chain.

25 As defined hereinbefore, adjacent carbon atoms in any (2-6C)alkylene chain within a  
R<sup>1</sup> or R<sup>6</sup> group may be optionally separated by the insertion into the chain of a group such as  
O, CON(R<sup>12</sup>) or CON(R<sup>23</sup>) respectively, and C≡C. For example, insertion of an O atom into  
the alkylene chain within a 4-methoxybutoxy group gives rise to, for example, a  
2-(2-methoxyethoxy)ethoxy group, for example, insertion of a C≡C group into the ethylene  
30 chain within a 2-hydroxyethoxy group gives rise to a 4-hydroxybut-2-ynyloxy group and, for  
example, insertion of a CONH group into the ethylene chain within a 3-methoxypropoxy group  
gives rise to, for example, a 2-(2-methoxyacetamido)ethoxy group.

- 21 -

When, as defined hereinbefore, any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> or R<sup>6</sup> group optionally bears on each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more halogeno or (1-8C)alkyl substituents, there is suitably 1 halogeno or (1-8C)alkyl substituent present on each said CH group, there are suitably 1 or 2 such substituents present on each said CH<sub>2</sub> group and there are  
 5 suitably 1, 2 or 3 such substituents present on each said CH<sub>3</sub> group.

When, as defined hereinbefore, any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> or R<sup>6</sup> group optionally bears on each said CH, CH<sub>2</sub> or CH<sub>3</sub> group a substituent as defined hereinbefore, suitable R<sup>1</sup> or R<sup>6</sup> groups so formed include, for example, hydroxy-substituted (1-8C)alkyl groups such as hydroxymethyl, 1-hydroxyethyl and 2-hydroxyethyl, hydroxy-substituted  
 10 (1-6C)alkoxy groups such as 2-hydroxypropoxy and 3-hydroxypropoxy, (1-6C)alkoxy-substituted (1-6C)alkoxy groups such as 2-methoxyethoxy and 3-ethoxypropoxy, hydroxy-substituted amino-(2-6C)alkoxy groups such as 3-amino-2-hydroxypropoxy, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkoxy groups such as 2-hydroxy-3-methylaminopropoxy, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkoxy groups such  
 15 as 3-dimethylamino-2-hydroxypropoxy, hydroxy-substituted amino-(2-6C)alkylamino groups such as 3-amino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkylamino groups such as 2-hydroxy-3-methylaminopropylamino and hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkylamino groups such as 3-dimethylamino-2-hydroxypropylamino.

20 When, as defined hereinbefore, any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> or R<sup>6</sup> group optionally bears on each said CH, CH<sub>2</sub> or CH<sub>3</sub> group a substituent as defined hereinbefore, suitable R<sup>1</sup> or R<sup>6</sup> groups so formed also include, for example, hydroxy-substituted (1-6C)alkylamino-(1-6C)alkyl groups such as 2-hydroxy-3-methylaminopropyl and 2-hydroxyethylaminomethyl and hydroxy-substituted di-[(1-6C)alkyl]amino-(1-6C)alkyl  
 25 groups such as 3-dimethylamino-2-hydroxypropyl and di-(2-hydroxyethyl)aminomethyl.

It is further to be understood that when, as defined hereinbefore, any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> or R<sup>6</sup> group optionally bears on each said CH, CH<sub>2</sub> or CH<sub>3</sub> group a substituent as defined hereinbefore, such an optional substituent may be present on a CH, CH<sub>2</sub> or CH<sub>3</sub> group within the hereinbefore defined substituents that may be present on an aryl,  
 30 heteroaryl or heterocyclyl group within a R<sup>1</sup> or R<sup>6</sup> group. For example, if the R<sup>1</sup> or R<sup>6</sup> group includes an aryl or heteroaryl group that is substituted by a (1-8C)alkyl group, the (1-8C)alkyl group may be optionally substituted on a CH, CH<sub>2</sub> or CH<sub>3</sub> group therein by one of the hereinbefore defined substituents therefor. For example, if the R<sup>1</sup> or R<sup>6</sup> group includes a

- 22 -

heteroaryl group that is substituted by, for example, a (1-6C)alkylamino-(1-6C)alkyl group, the terminal CH<sub>3</sub> group of the (1-6C)alkylamino group may be further substituted by, for example, a (1-6C)alkylsulphonyl group or a (2-6C)alkanoyl group. For example, the R<sup>1</sup> or R<sup>6</sup> group may be a heteroaryl group such as a thienyl group that is substituted by a

5 *N*-(2-methylsulphonylethyl)aminomethyl group such that R<sup>1</sup> or R<sup>6</sup> is, for example, a 5-[*N*-(2-methylsulphonylethyl)aminomethyl]thien-2-yl group. Further, for example, if the R<sup>1</sup> or R<sup>6</sup> group includes a heterocyclyl group such as a piperidinyl or piperazinyl group that is substituted on a nitrogen atom thereof by, for example, a (2-6C)alkanoyl group, the terminal CH<sub>3</sub> group of the (2-6C)alkanoyl group may be further substituted by, for example, a

10 di-[(1-6C)alkyl]amino group. For example, the R<sup>1</sup> or R<sup>6</sup> group may be a *N*-(2-dimethylaminoacetyl)piperidin-4-yl group or a 4-(2-dimethylaminoacetyl)piperazin-1-yl group. Further, for example, if the R<sup>1</sup> or R<sup>6</sup> group includes a heterocyclyl group such as a azetidiny, piperidinyl or piperazinyl group that is substituted on a nitrogen atom thereof by, for example, a (2-6C)alkanoyl group, a CH<sub>2</sub> group of the (2-6C)alkanoyl group may be further

15 substituted by, for example, a hydroxy group. For example, the R<sup>1</sup> or R<sup>6</sup> group may be a *N*-(2-hydroxypropionyl)piperidin-4-yl group.

As defined hereinbefore, two R<sup>6</sup> groups together may form a bivalent group, for example OC(R<sup>18</sup>)<sub>2</sub>O, that spans adjacent ring positions on Ring A. When Ring A is, for example, a phenyl group, a suitable group so formed is a 2,3-methylenedioxyphenyl or a

20 3,4-methylenedioxyphenyl group. When a further optional R<sup>6</sup> group is present, for example a halogeno group, a suitable group so formed is, for example, a 6-fluoro-2,3-methylenedioxyphenyl group. Further, when Ring A is, for example, a phenyl group and two R<sup>6</sup> groups together form, for example, a OC(R<sup>18</sup>)<sub>2</sub>C(R<sup>18</sup>)<sub>2</sub> group, a suitable group so formed is, for example, a 2,3-dihydrobenzofuran-5-yl group or a 2,3-dihydrobenzofuran-6-yl

25 group. Further, when Ring A is, for example, a phenyl group and two R<sup>6</sup> groups together form, for example, a N(R<sup>19</sup>)C(R<sup>18</sup>)<sub>2</sub>C(R<sup>18</sup>)<sub>2</sub> group, a suitable group so formed is, for example, an indolin-5-yl group or a indolin-6-yl group. Further, when Ring A is, for example, a phenyl group and two R<sup>6</sup> groups together form, for example, a N(R<sup>18</sup>)CO.C(R<sup>18</sup>)<sub>2</sub> group, a suitable group so formed is, for example, a 2-oxoindolin-5-yl group or a 2-oxoindolin-6-yl group.

30 A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the Formula I

- 23 -

which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine. A further suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for  
5 example, a salt formed within the human or animal body after administration of a compound of the Formula I.

A suitable pharmaceutically-acceptable solvate of a compound of the Formula I is, for example, a hydrate such as a hemi-hydrate, a mono-hydrate, a di-hydrate or a tri-hydrate or an alternative quantity thereof.

10 The compounds of the invention may be administered in the form of a pro-drug, that is a compound that is broken down in the human or animal body to release a compound of the invention. A pro-drug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the invention. A pro-drug can be formed when the compound of the invention contains a suitable group or substituent to which a property-modifying group can  
15 be attached. Examples of pro-drugs include *in vivo* cleavable ester derivatives that may be formed at a carboxy group or a hydroxy group in a compound of the Formula I and *in vivo* cleavable amide derivatives that may be formed at a carboxy group or an amino group in a compound of the Formula I.

Accordingly, the present invention includes those compounds of the Formula I as  
20 defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a pro-drug thereof. Accordingly, the present invention includes those compounds of the Formula I that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of the Formula I may be a  
25 synthetically-produced compound or a metabolically-produced compound.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula I is one that is based on reasonable medical judgement as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity.

30 Various forms of pro-drug have been described, for example in the following documents :-

a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);



- b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985);
  - c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", by H. Bundgaard p. 113-191 (1991);
  - 5 d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
  - e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988);
  - f) N. Kakeya, *et al.*, Chem. Pharm. Bull., 32, 692 (1984);
  - g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volume 14; and
  - 10 h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.
- A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula I that possesses a carboxy group is, for example, an *in vivo* cleavable ester thereof. An *in vivo* cleavable ester of a compound of the Formula I containing a carboxy group is, for example, a pharmaceutically-acceptable ester which is cleaved in the human or animal body to produce the
- 15 parent acid. Suitable pharmaceutically-acceptable esters for carboxy include (1-6C)alkyl esters such as methyl, ethyl and *tert*-butyl, (1-6C)alkoxymethyl esters such as methoxymethyl esters, (1-6C)alkanoyloxymethyl esters such as pivaloyloxymethyl esters, 3-phthalidyl esters, (3-8C)cycloalkylcarbonyloxy-(1-6C)alkyl esters such as cyclopentylcarbonyloxymethyl and 1-cyclohexylcarbonyloxyethyl esters,
- 20 2-oxo-1,3-dioxolenylmethyl esters such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl esters and (1-6C)alkoxycarbonyloxy-(1-6C)alkyl esters such as methoxycarbonyloxymethyl and 1-methoxycarbonyloxyethyl esters.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula I that possesses a hydroxy group is, for example, an *in vivo* cleavable ester or ether thereof. An

25 *in vivo* cleavable ester or ether of a compound of the Formula I containing a hydroxy group is, for example, a pharmaceutically-acceptable ester or ether which is cleaved in the human or animal body to produce the parent hydroxy compound. Suitable pharmaceutically-acceptable ester forming groups for a hydroxy group include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters). Further suitable pharmaceutically-acceptable ester

30 forming groups for a hydroxy group include (1-10C)alkanoyl groups such as acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups, (1-10C)alkoxycarbonyl groups such as ethoxycarbonyl, *N,N*-[di-(1-4C)alkyl]carbamoyl, 2-dialkylaminoacetyl and 2-carboxyacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups

- 25 -

include aminomethyl, *N*-alkylaminomethyl, *N,N*-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(1-4C)alkylpiperazin-1-ylmethyl. Suitable pharmaceutically-acceptable ether forming groups for a hydroxy group include  $\alpha$ -acyloxyalkyl groups such as acetoxymethyl and pivaloyloxymethyl groups.

- 5 A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula I that possesses a carboxy group is, for example, an *in vivo* cleavable amide thereof, for example an amide formed with an amine such as ammonia, a (1-4C)alkylamine such as methylamine, a di-(1-4C)alkylamine such as dimethylamine, *N*-ethyl-*N*-methylamine or diethylamine, a (1-4C)alkoxy-(2-4C)alkylamine such as 2-methoxyethylamine, a phenyl-(1-4C)alkylamine  
10 such as benzylamine and amino acids such as glycine or an ester thereof.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula I that possesses an amino group is, for example, an *in vivo* cleavable amide derivative thereof. Suitable pharmaceutically-acceptable amides from an amino group include, for example an amide formed with (1-10C)alkanoyl groups such as an acetyl, benzoyl, phenylacetyl and  
15 substituted benzoyl and phenylacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, *N*-alkylaminomethyl, *N,N*-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(1-4C)alkylpiperazin-1-ylmethyl.

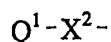
The *in vivo* effects of a compound of the Formula I may be exerted in part by one or  
20 more metabolites that are formed within the human or animal body after administration of a compound of the Formula I. As stated hereinbefore, the *in vivo* effects of a compound of the Formula I may also be exerted by way of metabolism of a precursor compound (a pro-drug).

Particular novel compounds of the invention include, for example, quinoline derivatives of the Formula I, or pharmaceutically-acceptable salts, solvates or pro-drugs  
25 thereof, wherein, unless otherwise stated, each of  $X^1$ , p,  $R^1$ , q,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , Ring A, r and  $R^6$  has any of the meanings defined hereinbefore or in paragraphs (a) to (ww) hereinafter :-

- (a)  $X^1$  is O or NH;
- (b)  $X^1$  is O;
- (c)  $X^1$  is NH;
- 30 (d) p is 1, 2 or 3, and each  $R^1$  group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl,

- 26 -

(1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or from a group of the formula :

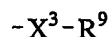


wherein  $X^2$  is a direct bond or is selected from O,  $N(R^8)$ ,  $CON(R^8)$ ,  $N(R^8)CO$  and  $OC(R^8)_2$

5 wherein  $R^8$  is hydrogen or (1-8C)alkyl, and  $Q^1$  is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within a substituent on  $R^1$  optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-8C)alkyl,

10 (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino and *N*-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the formula :



15 wherein  $X^3$  is a direct bond or is selected from O and  $N(R^{10})$ , wherein  $R^{10}$  is hydrogen or (1-8C)alkyl, and  $R^9$  is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkylsulphonyl-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or *N*-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl, or from a group of the formula :

20  $-X^4 - Q^2$

wherein  $X^4$  is a direct bond or is selected from O, CO and  $N(R^{11})$ , wherein  $R^{11}$  is hydrogen or (1-8C)alkyl, and  $Q^2$  is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-8C)alkyl and (1-6C)alkoxy,

25 and wherein any heterocyclyl group within a substituent on  $R^1$  optionally bears a (1-3C)alkylenedioxy group,

and wherein any heterocyclyl group within a substituent on  $R^1$  optionally bears 1 or 2 oxo substituents,

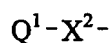
and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a  $R^1$  substituent optionally bears on  
30 each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more halogeno or (1-8C)alkyl groups and/or a substituent selected from hydroxy, amino, cyano, carboxy, carbamoyl, ureido, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl,

- 27 -

*N,N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

5 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a  $R^1$  substituent are optionally separated by the insertion into the chain of a group selected from O,  $N(R^{12})$ ,  $CON(R^{12})$ ,  $N(R^{12})CO$ ,  $CH=CH$  and  $C\equiv C$  wherein  $R^{12}$  is hydrogen or (1-8C)alkyl, or, when the inserted group is  $N(R^{12})$ ,  $R^{12}$  may also be (2-6C)alkanoyl;

(e) p is 1 or 2 and one  $R^1$  group may be a 3-cyano group and the other  $R^1$  group may be  
 10 located at the 5-, 6- or 7-position, or p is 2 or 3 and one  $R^1$  group may be a 3-cyano group and the other  $R^1$  groups, which may be the same or different, are located at the 5- and 7-positions or at the 6- and 7-positions and each other  $R^1$  group is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, ethyl, propyl, butyl, vinyl, allyl, but-3-enyl, ethynyl, 2-propynyl, but-3-ynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, allyloxy,  
 15 but-3-enyloxy, ethynyloxy, 2-propynyloxy, but-3-ynyloxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino and dipropylamino, or from a group of the formula :

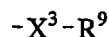


wherein  $X^2$  is a direct bond or is selected from O, NH, CONH, NHCO and  $OCH_2$  and  $Q^1$  is  
 20 phenyl, benzyl, cyclopropylmethyl, 2-thienyl, 1-imidazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 2-, 3- or 4-pyridyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, 2-(1,2,4-triazolyl)ethyl, 3-(1,2,4-triazolyl)propyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 3-(2-, 3- or 4-pyridyl)propyl, tetrahydrofuran-3-yl, 3- or 4-tetrahydropyranyl,  
 25 1-, 2- or 3-pyrrolidinyl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl,  
 30 4-pyrrolidin-1-ylbutyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, 2-piperidin-3-ylethyl,

- 28 -

3-piperidin-3-ylpropyl, 2-piperidin-4-ylethyl, 3-piperidin-4-ylpropyl,  
 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-(1,2,3,6-tetrahydropyridin-  
 1-yl)ethyl, 3-(1,2,3,6-tetrahydropyridin-1-yl)propyl, 4-(1,2,3,6-tetrahydropyridin-1-yl)butyl,  
 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 4-piperazin-1-ylbutyl, 2-homopiperazin-  
 5 1-ylethyl or 3-homopiperazin-1-ylpropyl,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within a  
 substituent on R<sup>1</sup> optionally bears 1, 2 or 3 substituents, which may be the same or different,  
 selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, allyl,  
 2-propynyl, methoxy, methylsulphonyl, methylamino, dimethylamino, acetyl, propionyl,  
 10 isobutyryl, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylenedioxy, ethylenedioxy and  
 isopropylidenedioxy, or optionally bears 1 substituent selected from a group of the formula :



wherein X<sup>3</sup> is a direct bond or is selected from O and NH and R<sup>9</sup> is 2-fluoroethyl,  
 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, 3,3-difluoropropyl,  
 15 3,3,3-trifluoropropyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl,  
 cyanomethyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl,  
 2-methylaminoethyl, 3-methylaminopropyl, 2-ethylaminoethyl, 3-ethylaminopropyl,  
 dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetamidomethyl or  
*N*-methylacetamidomethyl, and from a group of the formula :



wherein X<sup>4</sup> is a direct bond or is selected from O, CO and NH and Q<sup>2</sup> is  
 pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, morpholinomethyl,  
 2-morpholinoethyl, 3-morpholinopropyl, piperidinomethyl, 2-piperidinoethyl,  
 3-piperidinopropyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, each  
 25 of which optionally bears 1 or 2 substituents, which may be the same or different, selected  
 from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2  
 oxo substituents,

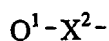
and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on  
 30 each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more fluoro, chloro or methyl groups or a substituent  
 selected from hydroxy, amino, cyano, methoxy, methylsulphonyl, methylamino,  
 dimethylamino, diisopropylamino, *N*-ethyl-*N*-methylamino, *N*-isopropyl-*N*-methylamino,  
 acetyl, acetamido and *N*-methylacetamido,

- 29 -

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R<sup>1</sup> substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), N(COMe), CONH, NHCO, CH=CH and C≡C;

(f) each of p and R<sup>1</sup> has any of the meanings defined in paragraphs (d) and (e)

5 hereinbefore except that when R<sup>1</sup> is a group of the formula :



X<sup>2</sup> may not be a direct bond;

(g) p is 1 or 2 and one R<sup>1</sup> group may be a 3-cyano group and the other R<sup>1</sup> group may be located at the 5-, 6- or 7-position, or p is 2 or 3 and one R<sup>1</sup> group may be a 3-cyano group and  
 10 the other R<sup>1</sup> groups, which may be the same or different, are located at the 5- and 7-positions or at the 6- and 7-positions and each other R<sup>1</sup> group is selected from cyano, hydroxy, amino, methyl, ethyl, propyl, butyl, vinyl, ethynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, but-3-enyloxy, methylamino, ethylamino, dimethylamino, diethylamino, cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy,  
 15 tetrahydropyran-4-yloxy, cyclopropylmethoxy, 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 3-(1,2,4-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, pyrid-4-ylmethoxy, 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy,  
 20 pyrrolidin-1-yl, morpholino, piperidino, piperazin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy,  
 25 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 4-(1,2,3,6-tetrahydropyridin-1-yl)butoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy,  
 30 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, 2-pyrrolidin-1-ylethylamino, 3-pyrrolidin-1-ylpropylamino, 4-pyrrolidin-1-ylbutylamino, pyrrolidin-3-ylamino,

- 30 -

- pyrrolidin-2-ylmethylamino, 2-pyrrolidin-2-ylethylamino, 3-pyrrolidin-2-ylpropylamino, 2-morpholinoethylamino, 3-morpholinopropylamino, 4-morpholinobutylamino, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethylamino, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylamino, 2-piperidinoethylamino, 3-piperidinopropylamino, 5 4-piperidinobutylamino, piperidin-3-ylamino, piperidin-4-ylamino, piperidin-3-ylmethylamino, 2-piperidin-3-ylethylamino, piperidin-4-ylmethylamino, 2-piperidin-4-ylethylamino, 2-homopiperidin-1-ylethylamino, 3-homopiperidin-1-ylpropylamino, 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino, 4-piperazin-1-ylbutylamino, 2-homopiperazin-1-ylethylamino or 10 3-homopiperazin-1-ylpropylamino,

- and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, ethoxy, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylenedioxy, 15 ethylidenedioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally *N*-substituted with allyl, 2-propynyl, methylsulphonyl, ethylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 20 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and 25 methoxy,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 oxo substituents,

- and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more fluoro, chloro or methyl groups or a substituent 30 selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, *N*-ethyl-*N*-methylamino, *N*-isopropyl-*N*-methylamino, *N*-methyl-*N*-propylamino, acetamido and *N*-methylacetamido,

- 31 -

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R<sup>1</sup> substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CH=CH and C≡C;

- (h) p is 1 or 2 and one R<sup>1</sup> group may be a 3-cyano group and the other R<sup>1</sup> group is located  
 5 at the 7-position, or p is 2 or 3 and one R<sup>1</sup> group may be a 3-cyano group and the other R<sup>1</sup>  
 groups, which may be the same or different, are located at the 6- and 7-positions and each other  
 R<sup>1</sup> group is selected from cyano, hydroxy, amino, methyl, ethyl, methoxy, ethoxy, propoxy,  
 isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino,  
 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy,  
 10 pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy,  
 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-  
 4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy,  
 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy,  
 piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy,  
 15 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy,  
 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy,  
 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2  
 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl,  
 20 hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidenedioxy and  
 isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl,  
 piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally *N*-substituted  
 with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl,  
 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

25 and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2  
 oxo substituents,

and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on  
 each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from  
 hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino,  
 30 *N*-ethyl-*N*-methylamino and *N*-isopropyl-*N*-methylamino,



- 32 -

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R<sup>1</sup> substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C;

- (i) p is 1 or 2 and one R<sup>1</sup> group may be a 3-cyano group and the other R<sup>1</sup> group is located at the 5-position, or p is 2 or 3 and one R<sup>1</sup> group may be a 3-cyano group and the other R<sup>1</sup> groups, which may be the same or different, are located at the 5- and 7-positions and each other R<sup>1</sup> group is selected from hydroxy, amino, methyl, ethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, 3-piperidinyloxy, 4-piperidinyloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy,

- and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidenedioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally *N*-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 oxo substituents,

- and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, *N*-ethyl-*N*-methylamino and *N*-isopropyl-*N*-methylamino,

- 33 -

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R<sup>1</sup> substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C;

- (j) p is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 6- and 7-positions and the R<sup>1</sup> group at the 6-position is selected from cyano, hydroxy, methoxy, ethoxy and propoxy, and the R<sup>1</sup> group at the 7-position is selected from methoxy, ethoxy, propoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

- and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidenedioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally *N*-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

- and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 oxo substituents,

- and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, *N*-ethyl-*N*-methylamino and *N*-isopropyl-*N*-methylamino;

- (k) p is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 5- and 7-positions and the R<sup>1</sup> group at the 5-position is selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, pyrrolidin-3-yloxy,

- 34 -

pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, 4-piperidinyloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy, and the R<sup>1</sup> group at the 7-position is selected from hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy,

5 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, 2-piperidin-3-ylethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-

10 1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and

15 isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally *N*-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2

20 oxo substituents,

and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, *N*-ethyl-*N*-methylamino and *N*-isopropyl-*N*-methylamino;

25 (l) q is 0;

(m) q is 1 or 2 and each R<sup>2</sup> group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

(n) q is 1 or 2 and each R<sup>2</sup> group, which may be the same or different, is selected from

30 fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino;

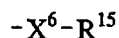
(o) q is 1 and the R<sup>2</sup> group is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino;

- 35 -

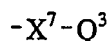
- (p)  $R^3$  is hydrogen, methyl or ethyl;
- (q)  $R^3$  is hydrogen;
- (r)  $R^4$  is hydrogen, methyl, ethyl, propyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, 2-hydroxyethyl, 5 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-cyanoethyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-ethylaminoethyl, 3-ethylaminopropyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetamidomethyl or *N*-methylacetamidomethyl;
- 10 (s)  $R^4$  is hydrogen, methyl or ethyl;
- (t)  $R^4$  is hydrogen;
- (u)  $R^3$  and  $R^4$  together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group;
- (v)  $R^5$  is hydrogen, methyl, ethyl, propyl, allyl, 2-propynyl, 2-fluoroethyl, 15 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-cyanoethyl or 3-cyanopropyl;
- (w)  $R^5$  is hydrogen, methyl or ethyl;
- (x)  $R^5$  is hydrogen;
- 20 (y) Ring A is a 6-membered monocyclic aryl ring or a 5- or 6-membered monocyclic heteroaryl ring with up to three ring heteroatoms selected from oxygen, nitrogen and sulphur;
- (z) Ring A is a phenyl ring;
- (aa) Ring A is a 6-membered monocyclic heteroaryl ring with up to three nitrogen heteroatoms;
- 25 (bb) Ring A is a 5-membered monocyclic heteroaryl ring with up to three ring heteroatoms selected from oxygen, nitrogen and sulphur;
- (cc) Ring A is a phenyl, furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl ring;
- (dd) Ring A is a phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl ring;
- 30 (ee) when Ring A is a 6-membered ring, and one or two  $R^6$  groups are present, one  $R^6$  group is located at the 3- or 4-position (relative to the  $\text{CON}(R^5)$  group);
- (ff) when Ring A is a 5-membered ring, and one or two  $R^6$  groups are present, one  $R^6$  group is located at the 3-position (relative to the  $\text{CON}(R^5)$  group);

- 36 -

- (gg) Ring A is a phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl ring that bears one or two  $R^6$  groups and one  $R^6$  group is located at the 3- or 4-position (relative to the  $CON(R^5)$  group);
- (hh) Ring A is a 9- or 10-membered bicyclic heteroaryl ring with up to three ring  
 5 heteroatoms selected from oxygen, nitrogen and sulphur;
- (ii) Ring A is a benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzotriazolyl, 1*H*-pyrrolo[3,2-*b*]pyridinyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl or naphthyridinyl ring;
- (jj) Ring A is a indolyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl,  
 10 benzotriazolyl, quinolyl, isoquinolyl, quinoxalinyl or naphthyridinyl ring;
- (kk)  $r$  is 1, 2 or 3 and each  $R^6$  group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoylamino and *N*-(1-6C)alkyl-(2-6C)alkanoylamino;
- 15 (ll)  $r$  is 1 or 2 and each  $R^6$  group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino;
- (mm)  $r$  is 1 and the  $R^6$  group is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino;
- 20 (nn)  $r$  is 1, 2 or 3 and one  $R^6$  group is a group of the formula :



- wherein  $X^6$  is a direct bond or is selected from O and  $N(R^{16})$ , wherein  $R^{16}$  is hydrogen or (1-8C)alkyl, and  $R^{15}$  is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, mercapto-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, (1-6C)alkylsulphinyl-(1-6C)alkyl,  
 25 (1-6C)alkylsulphonyl-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, *N*-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, *N*-(1-6C)alkylcarbamoyl-(1-6C)alkyl or *N,N*-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl provided that, when  $X^6$  is O or  
 30  $N(R^{16})$ , there are at least two carbon atoms between  $X^6$  and any heteroatom in the  $R^{15}$  group, or one  $R^6$  group is a group of the formula :

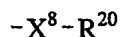


- 37 -

wherein  $X^7$  is a direct bond or is selected from O,  $N(R^{17})$ ,  $CON(R^{17})$ ,  $N(R^{17})CO$  and  $C(R^{17})_2O$ , wherein each  $R^{17}$  is hydrogen or (1-8C)alkyl, and  $Q^3$  is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl provided that, when  $X^7$  is selected from O,  $N(R^{17})$ ,  $CON(R^{17})$  or  $C(R^{17})_2O$ , there are at least two carbon atoms between  $X^7$  and any heteroatom in  $Q^3$  that is not in a heteroaryl ring,

and any other  $R^6$  group that is present is selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoylamino and *N*-(1-6C)alkyl-  
 10 (2-6C)alkanoylamino,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within an  $R^6$  group optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or  
 15 from a group of the formula :

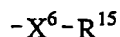


wherein  $X^8$  is a direct bond or is selected from O and  $N(R^{21})$ , wherein  $R^{21}$  is hydrogen or (1-8C)alkyl, and  $R^{20}$  is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or  
 20 di-[(1-6C)alkyl]amino-(1-6C)alkyl,

and wherein any heterocyclyl group within an  $R^6$  group optionally bears 1 or 2 oxo or thioxo substituents,

and wherein any CH,  $CH_2$  or  $CH_3$  group within an  $R^6$  group optionally bears on each said CH,  $CH_2$  or  $CH_3$  group one or more halogeno or (1-8C)alkyl substituents and/or a  
 25 substituent selected from hydroxy, amino, cyano, carboxy, carbamoyl, ureido, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino and *N*-(1-6C)alkyl-  
 (2-6C)alkanoylamino;

30 (oo)  $r$  is 1, 2 or 3 and one  $R^6$  group is a group of the formula :



wherein  $X^6$  is a direct bond or is selected from O and  $N(R^{16})$ , wherein  $R^{16}$  is hydrogen or (1-8C)alkyl, and  $R^{15}$  is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkylthio-

- 38 -

(1-6C)alkyl, (1-6C)alkylsulphinyl-(1-6C)alkyl, (1-6C)alkylsulphonyl-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, *N*-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl, aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, provided that, when  $X^6$  is O or  $N(R^{16})$ , there are at least two carbon atoms between  $X^6$  and any heteroatom in the  $R^{16}$  group, and any other  $R^6$  group that is present is selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoylamino and *N*-(1-6C)alkyl-(2-6C)alkanoylamino,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the  $R^6$  group optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-8C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or from a group of the formula :



wherein  $X^8$  is a direct bond and  $R^{20}$  is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl,

and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within the  $R^6$  group optionally bears on each said CH, CH<sub>2</sub> or CH<sub>3</sub> group 1, 2 or 3 halogeno or (1-8C)alkyl substituents and/or a substituent selected from hydroxy, amino, cyano, (3-8C)alkenyl, (3-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoylamino and *N*-(1-6C)alkyl-(2-6C)alkanoylamino;

(pp)  $r$  is 1, 2 or 3 and one  $R^6$  group is a group of the formula :



wherein  $X^6$  is a direct bond or is selected from O and  $N(R^{16})$ , wherein  $R^{16}$  is hydrogen or (1-8C)alkyl, and  $R^{15}$  is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, provided that, when  $X^6$  is O or  $N(R^{16})$ , there are at least two carbon atoms between  $X^6$  and any heteroatom in the  $R^{15}$  group,

- 39 -

and any other R<sup>6</sup> group that is present is selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-8C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoylamino and *N*-(1-6C)alkyl-(2-6C)alkanoylamino,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the R<sup>6</sup> group optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, (1-8C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, hydroxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl;

(qq) *r* is 1 or 2 and one R<sup>6</sup> group is a group of the formula :



wherein X<sup>6</sup> is a direct bond or is selected from O, NH and N(Me), and R<sup>15</sup> is hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxy-1-methylethyl, 3-hydroxypropyl, cyanomethyl, 1-cyanoethyl, 2-cyanoethyl, 1-cyano-1-methylethyl, 3-cyanopropyl, aminomethyl, 1-aminoethyl, 2-aminoethyl, 1-amino-1-methylethyl, 3-aminopropyl, methylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 1-methylamino-1-methylethyl, 3-methylaminopropyl, ethylaminomethyl, 1-ethylaminoethyl, 2-ethylaminoethyl, 1-ethylamino-1-methylethyl, 3-ethylaminopropyl, dimethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl, 1-dimethylamino-1-methylethyl, 3-dimethylaminopropyl, phenyl, benzyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, furyl, thienyl, oxazolyl, imidazolyl, thiazolyl, pyridyl, pyrimidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrrolinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, indolinyl, isoindolinyl, pyrrolinylmethyl, pyrrolidinylmethyl, 2-pyrrolidinylethyl, 3-pyrrolidinylpropyl, imidazolidinylmethyl, pyrazolidinylmethyl, morpholinylmethyl, 2-(morpholinyl)ethyl, 3-(morpholinyl)propyl, tetrahydro-1,4-thiazinylmethyl, 2-(tetrahydro-1,4-thiazinyl)ethyl, 3-(tetrahydro-1,4-thiazinyl)propyl, piperidinylmethyl, 2-(piperidinyl)ethyl, 3-(piperidinyl)propyl, homopiperidinylmethyl, piperazinylmethyl, 2-(piperazinyl)ethyl, 3-(piperazinyl)propyl or homopiperazinylmethyl, provided that, when X<sup>6</sup> is O, NH or N(Me), there are at least two carbon atoms between X<sup>6</sup> and any heteroatom in the R<sup>15</sup> group,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the R<sup>6</sup> group optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, ethoxy, methylamino, dimethylamine, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, aminomethyl, 2-aminoethyl,

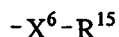


- 40 -

3-aminopropyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, dimethylaminomethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl,

and any other R<sup>6</sup> group that is present is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino;

5 (rr) r is 1 or 2 and the first R<sup>6</sup> group is a group of the formula :



wherein X<sup>6</sup> is a direct bond or O and R<sup>15</sup> is hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 3-hydroxypropyl, cyanomethyl, 1-cyanoethyl, 2-cyanoethyl, 3-cyanopropyl, aminomethyl, 1-aminoethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 1-methylaminoethyl, 10 2-methylaminoethyl, 3-methylaminopropyl, dimethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, phenyl, benzyl, cyclopropyl, cyclopentyl, cyclohexyl, thienyl, imidazolyl, thiazolyl, thiadiazolyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, pyrrolidinylmethyl, 2-(pyrrolidinyl)ethyl, 3-(pyrrolidinyl)propyl, morpholinylmethyl, 15 2-(morpholinyl)ethyl, 3-(morpholinyl)propyl, piperidinylmethyl, 2-(piperidinyl)ethyl, 3-(piperidinyl)propyl, homopiperidinylmethyl, piperazinylmethyl, 2-(piperazinyl)ethyl, 3-(piperazinyl)propyl or homopiperazinylmethyl, provided that, when X<sup>6</sup> is O, there are at least two carbon atoms between X<sup>6</sup> and any heteroatom in the R<sup>15</sup> group,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the R<sup>6</sup> 20 group optionally bears a substituent selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino and any such aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the R<sup>6</sup> group optionally bears a further substituent selected from hydroxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl,

25 and any second R<sup>6</sup> group that is present is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino;

(ss) r is 1 or 2 and the first R<sup>6</sup> group is selected from hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, cyanomethyl, 1-cyanoethyl, 2-cyanoethyl, aminomethyl, 1-aminoethyl, 2-aminoethyl, methylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 30 dimethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl, phenyl, benzyl, cyclopropyl, cyclopentyl, cyclohexyl, thienyl, imidazolyl, thiazolyl, thiadiazolyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, pyrrolidinylmethyl, 2-(pyrrolidinyl)ethyl, morpholinylmethyl,

- 41 -

2-(morpholinyl)ethyl, piperidinylmethyl, 2-(piperidinyl)ethyl, homopiperidinylmethyl, piperazinylmethyl, 2-(piperazinyl)ethyl and homopiperazinylmethyl,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the R<sup>6</sup> group optionally bears a substituent selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino and any such aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the R<sup>6</sup> group optionally bears a further substituent selected from hydroxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl,

and any second R<sup>6</sup> group that is present is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino;

(tt) two R<sup>6</sup> groups together form a bivalent group that spans adjacent ring positions on Ring A selected from OC(R<sup>18</sup>)<sub>2</sub>O, OC(R<sup>18</sup>)<sub>2</sub>C(R<sup>18</sup>)<sub>2</sub>, C(R<sup>18</sup>)<sub>2</sub>OC(R<sup>18</sup>)<sub>2</sub>, OC(R<sup>18</sup>)<sub>2</sub>N(R<sup>19</sup>), N(R<sup>19</sup>)C(R<sup>18</sup>)<sub>2</sub>N(R<sup>19</sup>), N(R<sup>19</sup>)C(R<sup>18</sup>)<sub>2</sub>C(R<sup>18</sup>)<sub>2</sub> and C(R<sup>18</sup>)<sub>2</sub>N(R<sup>19</sup>)C(R<sup>18</sup>)<sub>2</sub>, wherein each of R<sup>18</sup> and R<sup>19</sup> is hydrogen, (1-8C)alkyl, (2-8C)alkenyl or (2-8C)alkynyl;

(uu) two R<sup>6</sup> groups together form a bivalent group that spans adjacent ring positions on Ring A selected from OC(R<sup>18</sup>)<sub>2</sub>O, OC(R<sup>18</sup>)<sub>2</sub>C(R<sup>18</sup>)<sub>2</sub>O, C(R<sup>18</sup>)<sub>2</sub>OC(R<sup>18</sup>)<sub>2</sub>, OC(R<sup>18</sup>)<sub>2</sub>N(R<sup>19</sup>), N(R<sup>19</sup>)C(R<sup>18</sup>)<sub>2</sub>N(R<sup>19</sup>) and C(R<sup>18</sup>)<sub>2</sub>N(R<sup>19</sup>)C(R<sup>18</sup>)<sub>2</sub>, wherein each of R<sup>18</sup> and R<sup>19</sup> is hydrogen, methyl, ethyl or propyl;

(vv) two R<sup>6</sup> groups together form a bivalent group that spans adjacent ring positions on Ring A selected from OCH<sub>2</sub>O, OCH<sub>2</sub>CH<sub>2</sub>O, CH<sub>2</sub>OCH<sub>2</sub>, OCH<sub>2</sub>NH, NHCH<sub>2</sub>NH and CH<sub>2</sub>NHCH<sub>2</sub>; and

(ww) two R<sup>6</sup> groups together form a bivalent group that spans adjacent ring positions on Ring A selected from OCH<sub>2</sub>O and OCH<sub>2</sub>CH<sub>2</sub>O.

A particular compound of the invention is a quinoline derivative of the Formula I

wherein :-

X<sup>1</sup> is O or NH;

p is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 6- and 7-positions and the R<sup>1</sup> group at the 6-position is selected from cyano, hydroxy, methoxy, ethoxy and propoxy, and the R<sup>1</sup> group at the 7-position is selected from methoxy, ethoxy, propoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy,

- 42 -

2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy,  
 piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy,  
 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy,  
 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy,  
 5 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2  
 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl,  
 hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidenedioxy and  
 isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl,

10 piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally *N*-substituted  
 with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl,  
 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2  
 oxo substituents,

15 and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on  
 each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from  
 hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino,  
*N*-ethyl-*N*-methylamino and *N*-isopropyl-*N*-methylamino;

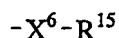
q is 0 or q is 1 and the R<sup>2</sup> group is selected from fluoro, chloro, trifluoromethyl,

20 hydroxy, amino, methyl, methoxy, methylamino and dimethylamino;

each of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is hydrogen;

Ring A is a phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl ring; and

r is 1 or 2 and one R<sup>6</sup> group is located at the 3- or 4-position (relative to the CON(R<sup>5</sup>)  
 group), and each R<sup>6</sup> group, which may be the same or different, is selected from fluoro, chloro,  
 25 trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino,  
 or the first R<sup>6</sup> group is located at the 3- or 4-position (relative to the CON(R<sup>5</sup>) group)  
 and is a group of the formula :



wherein X<sup>6</sup> is a direct bond or O and R<sup>15</sup> is hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl,  
 30 3-hydroxypropyl, cyanomethyl, 1-cyanoethyl, 2-cyanoethyl, 3-cyanopropyl, aminomethyl,  
 1-aminoethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 1-methylaminoethyl,  
 2-methylaminoethyl, 3-methylaminopropyl, dimethylaminomethyl, 1-dimethylaminoethyl,  
 2-dimethylaminoethyl, 3-dimethylaminopropyl, phenyl, benzyl, cyclopropyl, cyclopentyl,

- 43 -

cyclohexyl, thienyl, imidazolyl, thiazolyl, thiadiazolyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, pyrrolidinylmethyl, 2-(pyrrolidinyl)ethyl, 3-(pyrrolidinyl)propyl, morpholinylmethyl, 2-(morpholinyl)ethyl, 3-(morpholinyl)propyl, piperidinylmethyl, 2-(piperidinyl)ethyl, 3-(piperidinyl)propyl, homopiperidinylmethyl, piperazinylmethyl, 2-(piperazinyl)ethyl, 3-(piperazinyl)propyl or homopiperazinylmethyl, provided that, when X<sup>6</sup> is O, there are at least two carbon atoms between X<sup>6</sup> and any heteroatom in the R<sup>15</sup> group,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the R<sup>6</sup> group optionally bears a substituent selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino and any such aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the R<sup>6</sup> group optionally bears a further substituent selected from hydroxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl, and any second R<sup>6</sup> group that is present is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino; or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

A further particular compound of the invention is a quinoline derivative of the Formula I wherein :-

X<sup>1</sup> is O or NH;

p is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 6- and 7-positions and the R<sup>1</sup> group at the 6-position is selected from cyano, hydroxy, methoxy, ethoxy and propoxy, and the R<sup>1</sup> group at the 7-position is selected from methoxy, ethoxy, propoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl,

- 44 -

hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally *N*-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl,  
5 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 oxo substituents,

and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from  
10 hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, *N*-ethyl-*N*-methylamino and *N*-isopropyl-*N*-methylamino;

q is 0 or q is 1 and the R<sup>2</sup> group is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino;

each of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is hydrogen;

15 Ring A is a phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl ring; and

r is 1 or 2 and one R<sup>6</sup> group is located at the 3- or 4-position (relative to the CON(R<sup>5</sup>) group), and each R<sup>6</sup> group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino,

or the first R<sup>6</sup> group is located at the 3- or 4-position (relative to the CON(R<sup>5</sup>) group)  
20 and is selected from hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, cyanomethyl, 1-cyanoethyl, 2-cyanoethyl, aminomethyl, 1-aminoethyl, 2-aminoethyl, methylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, dimethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, pyrrolidinylmethyl, 2-(pyrrolidinyl)ethyl, 25 morpholinylmethyl, 2-(morpholinyl)ethyl, piperidinylmethyl, 2-(piperidinyl)ethyl, homopiperidinylmethyl, piperazinylmethyl, 2-(piperazinyl)ethyl and homopiperazinylmethyl,

and wherein any heterocyclyl group within the R<sup>6</sup> group optionally bears a substituent selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino and any such heterocyclyl group within the R<sup>6</sup> group optionally bears a  
30 further substituent selected from hydroxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl,

and any second R<sup>6</sup> group that is present is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino;

- 45 -

or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

A further particular compound of the invention is a quinoline derivative of the Formula I wherein :-

X<sup>1</sup> is O;

- 5 p is 2 and the first R<sup>1</sup> group is a 6-cyano or 6-methoxy group and the second R<sup>1</sup> group is located at the 7-position and is selected from methoxy, ethoxy, 2-methoxyethoxy, 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]ethoxy,
- 10 3-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy,
- 15 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-(4-hydroxypiperidin-1-yl)ethoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-
- 20 1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy, 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 2-(4-methylsulphonylpiperazin-1-yl)ethoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 4-(4-acetylpiperazin-1-yl)butoxy, 2-(4-isobutyrylpiperazin-1-yl)ethoxy, 3-(4-isobutyrylpiperazin-1-yl)propoxy,
- 25 4-(4-isobutyrylpiperazin-1-yl)butoxy, 2-[4-(2-fluoroethyl)piperazin-1-yl]ethoxy, 3-[4-(2-fluoroethyl)piperazin-1-yl]propoxy, 2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethoxy, 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy, 2-(4-pyridyloxy)ethoxy, 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy;
- 30 q is 0;
- each of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is hydrogen;
- Ring A is a phenyl or pyridyl ring; and

- 46 -

r is 1 or 2 and one R<sup>6</sup> group is located at the 3- or 4-position (relative to the CON(R<sup>5</sup>) group), and each R<sup>6</sup> group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino,

or the first R<sup>6</sup> group is located at the 3- or 4-position (relative to the CON(R<sup>5</sup>) group)  
5 and is selected from hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, cyanomethyl, 1-cyanoethyl, 2-cyanoethyl, aminomethyl, 1-aminoethyl, 2-aminoethyl, methylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, dimethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl, pyrrolidinylmethyl, morpholinylmethyl, piperidinylmethyl and piperazinylmethyl,

10 and wherein any heterocyclyl group within the R<sup>6</sup> group optionally bears a substituent selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino,

and any second R<sup>6</sup> group that is present is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino;

15 or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

A further particular compound of the invention is a quinoline derivative of the Formula I wherein :-

X<sup>1</sup> is O;

p is 2 and the first R<sup>1</sup> group is a 6-cyano or 6-methoxy group and the second R<sup>1</sup> group  
20 is located at the 7-position and is selected from methoxy, ethoxy and 2-methoxyethoxy;

q is 0;

each of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is hydrogen;

Ring A is phenyl; and

r is 1 or 2 and one R<sup>6</sup> group is located at the 3-position (relative to the CON(R<sup>5</sup>) group),  
25 and each R<sup>6</sup> group, which may be the same or different, is selected from fluoro, chloro, methoxy, methylamino and dimethylamino,

or the first R<sup>6</sup> group is located at the 3-position (relative to the CON(R<sup>5</sup>) group) and is selected from hydroxymethyl, 1-hydroxyethyl, aminomethyl, 1-aminoethyl, methylaminomethyl, 1-methylaminoethyl, dimethylaminomethyl and 1-dimethylaminoethyl,

30 and any second R<sup>6</sup> group that is present is selected from fluoro, chloro, methoxy, methylamino and dimethylamino;

or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

- 47 -

A further particular compound of the invention is a quinoline derivative of the Formula I wherein :-

$X^1$  is O or NH;

p is 2 and the  $R^1$  groups, which may be the same or different, are located at the 5- and  
 5 7-positions and the  $R^1$  group at the 5-position is selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, 4-piperidinyloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy, and the  $R^1$  group at the 7-position is selected from hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy,  
 10 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, 2-piperidin-3-ylethoxy, 2-piperidin-4-ylethoxy,  
 15 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein any heterocyclyl group within a substituent on  $R^1$  optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl,  
 20 hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a  $R^1$  substituent is optionally *N*-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

25 and wherein any heterocyclyl group within a substituent on  $R^1$  optionally bears 1 or 2 oxo substituents,

and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a  $R^1$  substituent optionally bears on each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino,  
 30 *N*-ethyl-*N*-methylamino and *N*-isopropyl-*N*-methylamino;

q is 0 or q is 1 and the  $R^2$  group is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino;

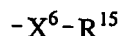
each of  $R^3$ ,  $R^4$  and  $R^5$  is hydrogen;



- 48 -

Ring A is a phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl ring; and

r is 1 or 2 and one R<sup>6</sup> group is located at the 3- or 4-position (relative to the CON(R<sup>5</sup>) group), and each R<sup>6</sup> group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino,  
 5 or the first R<sup>6</sup> group is located at the 3- or 4-position (relative to the CON(R<sup>5</sup>) group) and is a group of the formula :



wherein X<sup>6</sup> is a direct bond or O and R<sup>15</sup> is hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 3-hydroxypropyl, cyanomethyl, 1-cyanoethyl, 2-cyanoethyl, 3-cyanopropyl, aminomethyl,  
 10 1-aminoethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 3-methylaminopropyl, dimethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, phenyl, benzyl, cyclopropyl, cyclopentyl, cyclohexyl, thienyl, imidazolyl, thiazolyl, thiadiazolyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl,  
 15 pyrrolidinylmethyl, 2-(pyrrolidinyl)ethyl, 3-(pyrrolidinyl)propyl, morpholinylmethyl, 2-(morpholinyl)ethyl, 3-(morpholinyl)propyl, piperidinylmethyl, 2-(piperidinyl)ethyl, 3-(piperidinyl)propyl, homopiperidinylmethyl, piperazinylmethyl, 2-(piperazinyl)ethyl, 3-(piperazinyl)propyl or homopiperazinylmethyl, provided that, when X<sup>6</sup> is O, there are at least two carbon atoms between X<sup>6</sup> and any heteroatom in the R<sup>15</sup> group,  
 20 and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the R<sup>6</sup> group optionally bears a substituent selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino and any such aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the R<sup>6</sup> group optionally bears a further substituent selected from hydroxymethyl, cyanomethyl, aminomethyl,  
 25 methylaminomethyl and dimethylaminomethyl,

and any second R<sup>6</sup> group that is present is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino; or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

A further particular compound of the invention is a quinoline derivative of the  
 30 Formula I wherein :-

X<sup>1</sup> is O or NH;

p is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 5- and 7-positions and the R<sup>1</sup> group at the 5-position is selected from methoxy, ethoxy, propoxy,

- 49 -

isopropoxy, butoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, 4-piperidinyloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy, and the R<sup>1</sup> group at the 7-position is selected from hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy,

5 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, 2-piperidin-3-ylethoxy, 2-piperidin-4-ylethoxy,

10 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl,

15 hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally *N*-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

20 and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 oxo substituents,

and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino,

25 *N*-ethyl-*N*-methylamino and *N*-isopropyl-*N*-methylamino;

q is 0 or q is 1 and the R<sup>2</sup> group is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino;

each of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is hydrogen;

Ring A is a phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl ring; and

30 r is 1 or 2 and one R<sup>6</sup> group is located at the 3- or 4-position (relative to the CON(R<sup>5</sup>) group), and each R<sup>6</sup> group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino,

- 50 -

or the first R<sup>6</sup> group is located at the 3- or 4-position (relative to the CON(R<sup>5</sup>) group) and is selected from hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, cyanomethyl, 1-cyanoethyl, 2-cyanoethyl, aminomethyl, 1-aminoethyl, 2-aminoethyl, methylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, dimethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, pyrrolidinylmethyl, 2-(pyrrolidinyl)ethyl, morpholinylmethyl, 2-(morpholinyl)ethyl, piperidinylmethyl, 2-(piperidinyl)ethyl, homopiperidinylmethyl, piperazinylmethyl, 2-(piperazinyl)ethyl and homopiperazinylmethyl, and wherein any heterocyclyl group within the R<sup>6</sup> group optionally bears a substituent selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino and any such heterocyclyl group within the R<sup>6</sup> group optionally bears a further substituent selected from hydroxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl, and any second R<sup>6</sup> group that is present is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino; or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

A further particular compound of the invention is a quinoline derivative of the Formula I wherein :-

X<sup>1</sup> is O;

p is 1 and the R<sup>1</sup> group is located at the 5-position and is selected from methoxy, ethoxy, propoxy, isopropoxy, tetrahydropyran-4-yloxy, 4-piperidinyloxy and N-methylpiperidin-4-yloxy, or p is 2 and the first R<sup>1</sup> group is located at the 5-position and is selected from the group of substituents listed immediately above, and the second R<sup>1</sup> group is located at the 7-position and is selected from methoxy, ethoxy, 2-methoxyethoxy, 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]ethoxy, 3-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy, 2-(4-prop-2-ynylpiperazin-

- 51 -

1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 2-(4-isobutyrylpiperazin-1-yl)ethoxy, 3-(4-isobutyrylpiperazin-1-yl)propoxy, 2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethoxy and 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy;

5 q is 0;

each of  $R^3$ ,  $R^4$  and  $R^5$  is hydrogen;

Ring A is a phenyl or pyridyl ring; and

r is 1 or 2 and one  $R^6$  group is located at the 3- or 4-position (relative to the  $CON(R^5)$  group), and each  $R^6$  group, which may be the same or different, is selected from fluoro, chloro, 10 trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino, or the first  $R^6$  group is located at the 3- or 4-position (relative to the  $CON(R^5)$  group) and is selected from hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, cyanomethyl, 1-cyanoethyl, 2-cyanoethyl, aminomethyl, 1-aminoethyl, 2-aminoethyl, methylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, dimethylaminomethyl, 1-dimethylaminoethyl, 15 2-dimethylaminoethyl, pyrrolidinylmethyl, morpholinylmethyl, piperidinylmethyl and piperazinylmethyl,

and wherein any heterocyclyl group within the  $R^6$  group optionally bears a substituent selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino,

20 and any second  $R^6$  group that is present is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino; or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

A further particular compound of the invention is a quinoline derivative of the Formula I wherein :-

25  $X^1$  is O;

p is 2 and the first  $R^1$  group is a 5-methoxy group and the second  $R^1$  group is located at the 7-position and is selected from methoxy, ethoxy and 2-methoxyethoxy;

q is 0;

each of  $R^3$ ,  $R^4$  and  $R^5$  is hydrogen;

30 Ring A is phenyl; and

r is 1 or 2 and one  $R^6$  group is located at the 3-position (relative to the  $CON(R^5)$  group), and each  $R^6$  group, which may be the same or different, is selected from fluoro, chloro, methoxy, methylamino and dimethylamino,

- 52 -

or the first R<sup>6</sup> group is located at the 3-position (relative to the CON(R<sup>5</sup>) group) and is selected from hydroxymethyl, 1-hydroxyethyl, aminomethyl, 1-aminoethyl, methylaminomethyl, 1-methylaminoethyl, dimethylaminomethyl and 1-dimethylaminoethyl, and any second R<sup>6</sup> group that is present is selected from fluoro, chloro, methoxy, methylamino and dimethylamino; or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

Further particular compounds of the invention are quinoline derivatives of the Formula I wherein each of p, R<sup>1</sup>, X<sup>1</sup>, q, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and Ring A has any of the meanings defined hereinbefore in the various definitions of particular compounds of the invention provided that two R<sup>6</sup> groups together form a bivalent group that spans adjacent ring positions on Ring A selected from OCH<sub>2</sub>O, OCH<sub>2</sub>CH<sub>2</sub>O, CH<sub>2</sub>OCH<sub>2</sub>, OCH<sub>2</sub>NH, NHCH<sub>2</sub>NH and CH<sub>2</sub>NHCH<sub>2</sub>; or pharmaceutically-acceptable salts, solvates or pro-drugs thereof.

Further particular compounds of the invention are quinoline derivatives of the Formula I wherein each of p, R<sup>1</sup>, X<sup>1</sup>, q, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> has any of the meanings defined hereinbefore in the various definitions of particular compounds of the invention provided that Ring A is phenyl and two R<sup>6</sup> groups together form a OCH<sub>2</sub>O bivalent group that spans the 2,3- or 3,4-positions on said phenyl ring; or pharmaceutically-acceptable salts, solvates or pro-drugs thereof.

A further particular compound of the invention is a quinoline derivative of the Formula I wherein :-

X<sup>1</sup> is O;

p is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 6- and 7-positions and are selected from cyano, methoxy, ethoxy, propoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy and 2-(2-methoxyethoxy)ethoxy;

q is 0 or q is 1 and the R<sup>2</sup> group is fluoro, chloro, methyl or methoxy;

each of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is hydrogen;

Ring A is phenyl; and

r is 1 or 2 and the first R<sup>6</sup> group is located at the 3-position (relative to the CON(R<sup>5</sup>) group) and is selected from fluoro, chloro, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, cyclopropylamino, *N*-cyclopropyl-*N*-methylamino, hydroxymethyl, aminomethyl, methylaminomethyl, ethylaminomethyl, isopropylaminomethyl,

- 53 -

cyclopropylaminomethyl, dimethylaminomethyl, diethylaminomethyl, *N*-ethyl-*N*-methylaminomethyl, *N*-cyclopropyl-*N*-methylaminomethyl, azetidinylmethyl, pyrrolidinylmethyl, morpholinylmethyl, piperidinylmethyl, homopiperidinylmethyl, piperazinylmethyl and homopiperazinylmethyl,

5 and any second R<sup>6</sup> group that is present is selected from fluoro, chloro, methyl, ethyl, methoxy and ethoxy,

and wherein any heterocyclyl group within the R<sup>6</sup> group optionally bears a methyl, ethyl or hydroxymethyl substituent;  
or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

10 A further particular compound of the invention is a quinoline derivative of the Formula I wherein :-

X<sup>1</sup> is O;

p is 2 and the first R<sup>1</sup> group is a 6-cyano or 6-methoxy group and the second R<sup>1</sup> group is located at the 7-position and is selected from methoxy, ethoxy, 2-hydroxyethoxy and

15 2-methoxyethoxy;

q is 0 or q is 1 and the R<sup>2</sup> group is fluoro;

each of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is hydrogen;

Ring A is phenyl; and

r is 1 or 2 and the first R<sup>6</sup> group is located at the 3-position (relative to the CON(R<sup>5</sup>) group) and is selected from fluoro, chloro, methoxy, methylamino, ethylamino, dimethylamino, cyclopropylamino, hydroxymethyl, aminomethyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, isopropylaminomethyl, cyclopropylaminomethyl, dimethylaminomethyl, diethylaminomethyl, *N*-ethyl-*N*-methylaminomethyl, *N*-cyclopropyl-*N*-methylaminomethyl, azetidin-1-ylmethyl, pyrrolidin-1-ylmethyl, morpholinomethyl, piperidinomethyl and  
25 piperazin-1-ylmethyl,

and any second R<sup>6</sup> group that is present is selected from fluoro, chloro, methyl, ethyl, methoxy and ethoxy,

and wherein any heterocyclyl group within the R<sup>6</sup> group optionally bears a methyl, ethyl or hydroxymethyl substituent;

30 or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

A further particular compound of the invention is a quinoline derivative of the Formula I wherein :-

X<sup>1</sup> is O;

- 54 -

p is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 6- and 7-positions and are selected from cyano, methoxy, ethoxy, propoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy and 2-(2-methoxyethoxy)ethoxy;

5 q is 0 or q is 1 and the R<sup>2</sup> group is fluoro, chloro, methyl or methoxy;

each of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is hydrogen;

Ring A is pyridyl; and

r is 0, 1 or 2 and each R<sup>6</sup> group that is present is selected from fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, propyl, isopropyl, *tert*-butyl, cyclopropyl, cyclobutyl, 10 cyclopentyl, methoxy, ethoxy, methylamino, ethylamino, propylamino, isopropylamino, cyclopropylamino, 2-hydroxyethylamino, 2-methoxyethylamino, dimethylamino, *N*-cyclopropyl-*N*-methylamino, acetyl, hydroxymethyl, aminomethyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, isopropylaminomethyl, cyclopropylaminomethyl, dimethylaminomethyl, diethylaminomethyl, *N*-ethyl-*N*-methylaminomethyl, *N*-cyclopropyl- 15 *N*-methylaminomethyl, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, pyrrolidin-1-ylmethyl, morpholinomethyl, piperidinomethyl and piperazin-1-ylmethyl, and wherein any heterocyclyl group within the R<sup>6</sup> group optionally bears a methyl or ethyl substituent;

or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

20 A further particular compound of the invention is a quinoline derivative of the Formula I wherein :-

X<sup>1</sup> is O;

p is 2 and the first R<sup>1</sup> group is a 6-cyano or 6-methoxy group and the second R<sup>1</sup> group is located at the 7-position and is selected from methoxy, ethoxy, 2-hydroxyethoxy and 25 2-methoxyethoxy;

q is 0 or q is 1 and the R<sup>2</sup> group is fluoro;

each of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is hydrogen;

Ring A is 2-pyridyl; and

r is 1 or 2 and the first R<sup>6</sup> group is located at the 3-position (relative to the CON(R<sup>5</sup>) 30 group) and is selected from methylamino, ethylamino, propylamino, isopropylamino, cyclopropylamino, 2-hydroxyethylamino, 2-methoxyethylamino, dimethylamino, *N*-cyclopropyl-*N*-methylamino, pyrrolidin-1-yl, piperidino, morpholino and piperazin-1-yl,

- 55 -

and any second R<sup>6</sup> group that is present is selected from fluoro, chloro, methyl, ethyl, methoxy and ethoxy,

and wherein any heterocyclyl group within the R<sup>6</sup> group optionally bears a methyl or ethyl substituent;

5 or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

A further particular compound of the invention is a quinoline derivative of the Formula I wherein :-

X<sup>1</sup> is O;

p is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 6- and  
10 7-positions and are selected from cyano, methoxy, ethoxy, propoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy and 2-(2-methoxyethoxy)ethoxy;

q is 0 or q is 1 and the R<sup>2</sup> group is fluoro, chloro, methyl or methoxy;

each of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is hydrogen;

15 Ring A is selected from thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl and pyrazolyl; and

r is 0, 1 or 2 and each R<sup>6</sup> group that is present is selected from fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, propyl, isopropyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, methylamino, ethylamino, propylamino, isopropylamino,  
20 cyclopropylamino, 2-hydroxyethylamino, 2-methoxyethylamino, dimethylamino, *N*-cyclopropyl-*N*-methylamino, acetyl, hydroxymethyl, aminomethyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, isopropylaminomethyl, cyclopropylaminomethyl, dimethylaminomethyl, diethylaminomethyl, *N*-ethyl-*N*-methylaminomethyl, *N*-cyclopropyl-*N*-methylaminomethyl, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl,  
25 pyrrolidin-1-ylmethyl, morpholinomethyl, piperidinomethyl and piperazin-1-ylmethyl,

and wherein any heterocyclyl group within the R<sup>6</sup> group optionally bears a methyl or ethyl substituent;

or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

A further particular compound of the invention is a quinoline derivative of the  
30 Formula I wherein :-

X<sup>1</sup> is O;



- 56 -

p is 2 and the first R<sup>1</sup> group is a 6-cyano or 6-methoxy group and the second R<sup>1</sup> group is located at the 7-position and is selected from methoxy, ethoxy, 2-hydroxyethoxy and 2-methoxyethoxy;

q is 0 or q is 1 and the R<sup>2</sup> group is fluoro;

5 each of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is hydrogen;

Ring A is 2-thiazolyl, 2-oxazolyl, 3-isoxazolyl, 5-isoxazolyl, 2-imidazolyl, 3-pyrazolyl or 4-pyrazolyl; and

r is 0, 1 or 2 and each R<sup>6</sup> group that is present is selected from fluoro, chloro, cyano, methyl, ethyl, propyl, isopropyl, *tert*-butyl, cyclopropyl, methoxy, ethoxy and acetyl;

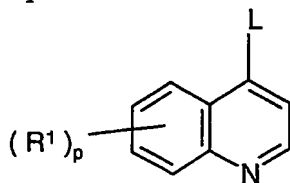
10 or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

Particular compounds of the invention are, for example, the quinoline derivatives of the Formula I that are disclosed within Example 1 and as Compound No. 1 within Example 2 that are set out hereinafter.

Further particular compounds of the invention are, for example, the quinoline  
15 derivatives of the Formula I that are disclosed as Compound No. 7 within Example 2, as Compound No. 8 within Example 3 and within Examples 4 and 5 that are set out hereinafter.

A quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a quinoline derivative  
20 of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, each of X<sup>1</sup>, p, R<sup>1</sup>, q, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, Ring A, r and R<sup>6</sup> has any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following  
25 representative process variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

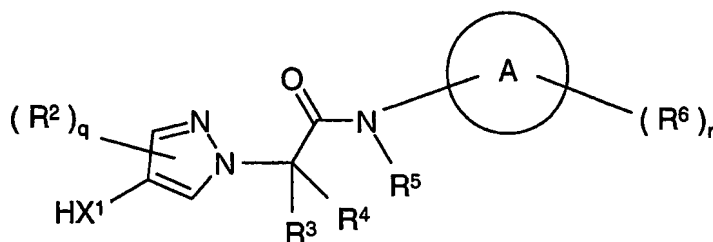
(a) The reaction of a quinoline of the Formula II



II

- 57 -

wherein L is a displaceable group and p and R<sup>1</sup> have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a pyrazole of the Formula III



III

wherein X<sup>1</sup>, q, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, Ring A, r and R<sup>6</sup> have any of the meanings defined hereinbefore  
 5 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed.

The reaction may conveniently be carried out in the presence of a suitable acid or in the presence of a suitable base. A suitable acid is, for example, an inorganic acid such as, for example, hydrogen chloride or hydrogen bromide. A suitable base is, for example, an organic  
 10 amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, *N*-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide, or, for example, an alkali metal amide, for example sodium hexamethyldisilazane, or, for  
 15 example, an alkali metal hydride, for example sodium hydride.

A suitable displaceable group L is, for example, a halogeno, alkoxy, aryloxy or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, pentafluorophenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as  
 20 methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxane, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for  
 25 example, 0 to 250°C, preferably in the range 0 to 120°C.

Typically, the quinoline of the Formula II may be reacted with a compound of the Formula III in the presence of an aprotic solvent such as *N,N*-dimethylformamide, conveniently in the presence of a base, for example potassium carbonate or sodium hexamethyldisilazane,

- 58 -

and at a temperature in the range, for example, 0 to 150°C, preferably in the range, for example, 0 to 70°C.

The quinoline derivative of the Formula I may be obtained from this process in the form of the free base or alternatively it may be obtained in the form of a salt with the acid of the formula H-L wherein L has the meaning defined hereinbefore. When it is desired to obtain the free base from the salt, the salt may be treated with a suitable base, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, *N*-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned are, of course, within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, and *tert*-butyl); lower alkoxy- lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower alkoxycarbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and 1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for

- 59 -

example trimethylsilyl and *tert*-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl). Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed cleavage.

- 5        Examples of hydroxy protecting groups include lower alkyl groups (for example *tert*-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example *tert*-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 10 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); tri(lower alkyl)silyl (for example trimethylsilyl and *tert*-butyldimethylsilyl) and aryl-lower alkyl (for example benzyl) groups.

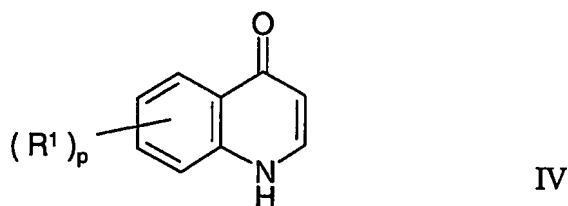
      Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower 15 alkoxycarbonyl (for example *tert*-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); trialkylsilyl (for example trimethylsilyl and *tert*-butyldimethylsilyl); alkylidene (for example methylenidene) and benzylenidene and substituted benzylenidene groups.

- 20        Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxycarbonyl.

      The reader is referred to Advanced Organic Chemistry, 4th Edition, by J. March, 25 published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents and to Protective Groups in Organic Synthesis, 2<sup>nd</sup> Edition, by T. Green *et al.*, also published by John Wiley & Son, for general guidance on protecting groups.

      Quinoline starting materials of the Formula II may be obtained by conventional procedures such as those disclosed in International Patent Applications WO 98/13350 and 30 WO 02/12226. For example, a 1,4-dihydroquinolin-4-one of the Formula IV

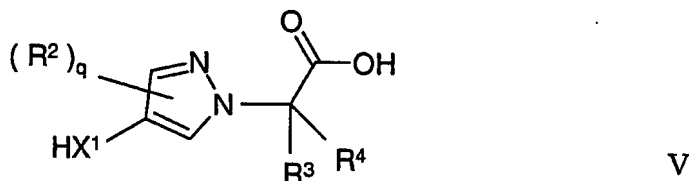
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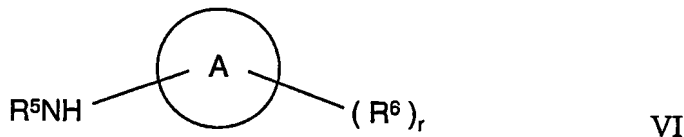
wherein p and R<sup>1</sup> have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a halogenating agent such as thionyl chloride, phosphoryl chloride or a mixture of carbon tetrachloride and triphenylphosphine  
 5 whereafter any protecting group that is present is removed.

The 4-chloroquinoline so obtained may be converted, if required, into a 4-pentafluorophenoxyquinoline by reaction with pentafluorophenol in the presence of a suitable base such as potassium carbonate and in the presence of a suitable solvent such as *N,N*-dimethylformamide.

10 Pyrazole starting materials of the Formula III may be obtained by conventional procedures, for example using procedures analogous to those described in International Patent Applications WO 02/00649, WO 03/055491 and PCT/GB2004/001614 (published subsequently as WO 2004/094410). For example, an acetic acid of the Formula V



15 or a reactive derivative thereof, wherein X<sup>1</sup>, q, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with an amine of the Formula VI



wherein R<sup>5</sup>, Ring A, r and R<sup>6</sup> have any of the meanings defined hereinbefore except that any  
 20 functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

A suitable reactive derivative of an acetic acid of the Formula V is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid with an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride

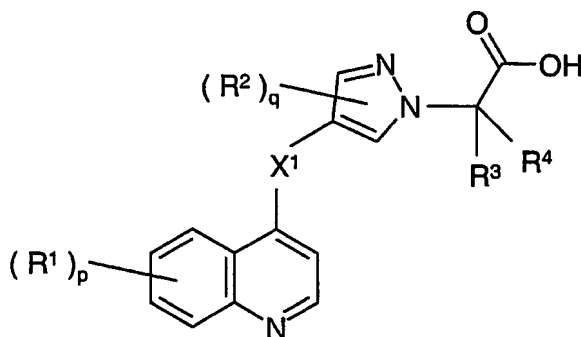
- 61 -

formed by the reaction of the acid with a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid with a phenol such as pentafluorophenol, with an ester such as pentafluorophenyl trifluoroacetate or with an alcohol such as methanol, ethanol, isopropanol, butanol or *N*-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid with an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid with a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid with a carbodiimide such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or with a uronium compound such as 2-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate(V) or 2-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxane, an aromatic solvent such as toluene. Conveniently, the reaction is conveniently carried out in the presence of a dipolar aprotic solvent such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 0 to 120°C, preferably at or near ambient temperature.

Acetic acid derivatives of the Formula V and amines of the Formula VI may be obtained by conventional procedures such as those disclosed in the Examples that are set out hereinafter.

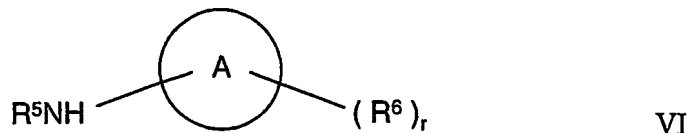
(b) The coupling, conveniently in the presence of a suitable base, of a quinoline of the Formula VII



VII

- 62 -

or a reactive derivative thereof as defined hereinbefore, wherein  $p$ ,  $R^1$ ,  $X^1$ ,  $q$ ,  $R^2$ ,  $R^3$  and  $R^4$  have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an amine of the Formula VI



- 5 wherein  $R^5$ , Ring A,  $r$  and  $R^6$  have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed.

- A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine,
- 10 *N*-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide, or, for example, an alkali metal amide, for example sodium hexamethyldisilazane, or, for example, an alkali metal hydride, for example sodium hydride.
- 15 The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxane, an aromatic solvent such as toluene. Conveniently, the reaction is conveniently carried out in the presence of a dipolar aprotic solvent such as
- 20 *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 0 to 120°C, preferably at or near ambient temperature.

Quinoline derivatives of the Formula VII and amines of the Formula VI may be obtained by conventional procedures such as those disclosed in the Examples that are set out

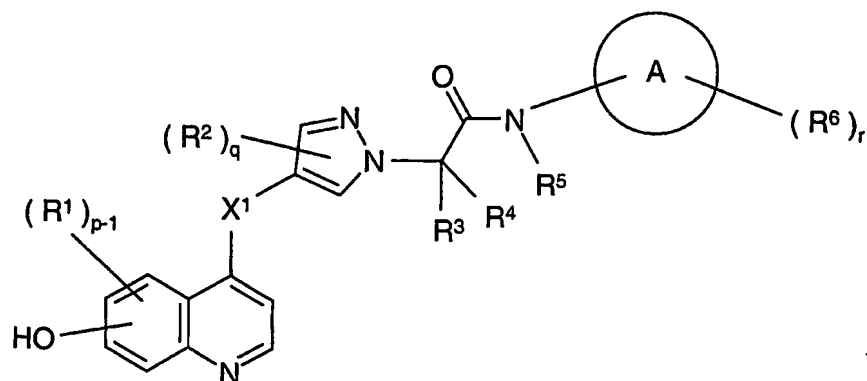
25 hereinafter.

(c) For the production of those compounds of the Formula I wherein at least one  $R^1$  group is a group of the formula



- wherein  $Q^1$  is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-
- 30 (1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group or an optionally

substituted alkyl group and  $X^2$  is an oxygen atom, the coupling, conveniently in the presence of a suitable dehydrating agent, of a quinoline of the Formula VIII



VIII

wherein each of  $p$ ,  $R^1$ ,  $X^1$ ,  $q$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , Ring A,  $r$  and  $R^6$  has any of the meanings defined  
 5 hereinbefore except that any functional group is protected if necessary, with an appropriate  
 alcohol wherein any functional group is protected if necessary, whereafter any protecting group  
 that is present is removed.

A suitable dehydrating agent is, for example, a carbodiimide reagent such as  
 dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or a mixture of  
 10 an azo compound such as diethyl or di-*tert*-butyl azodicarboxylate and a phosphine such as  
 triphenylphosphine. The reaction is conveniently carried out in the presence of a suitable inert  
 solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform  
 or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably  
 at or near ambient temperature.

15 Quinoline derivatives of the Formula VIII may be obtained by conventional procedures.

(d) For the production of those compounds of the Formula I wherein a  $R^6$  group is a group  
 of the formula  $-X^6-R^{15}$  wherein  $X^6$  has any of the meanings defined hereinbefore and  $R^{15}$  is an  
 amino-substituted (1-6C)alkyl group (such as a dimethylaminomethyl,  
 2-dimethylaminoethyl or 4-methylpiperazin-1-ylmethyl group), the reaction, conveniently in  
 20 the presence of a suitable base as defined hereinbefore, of a compound of the Formula I  
 wherein a  $R^6$  group is a group of the formula  $-X^6-R^{15}$  wherein  $R^{15}$  is a halogeno-substituted  
 (1-6C)alkyl group with an appropriate amine or with a nitrogen-containing heterocyclyl  
 compound.

The reaction is conveniently carried out in the presence of a suitable inert solvent or  
 25 diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 180°C,



- 64 -

conveniently in the range 20 to 120°C, more conveniently at or near ambient temperature.

Compounds of the Formula I wherein a  $R^6$  group is a group of the formula  $-X^6-R^{15}$  wherein  $R^{15}$  is a halogeno-substituted (1-6C)alkyl group may be obtained by any of the representative process variants (a), (b) or (c) that are described hereinbefore.

- 5 (e) For the production of those compounds of the Formula I wherein a  $R^6$  group is a group of the formula  $-X^6-R^{15}$  wherein  $X^6$  has any of the meanings defined hereinbefore and  $R^{15}$  is an amino-substituted (1-6C)alkyl group (such as a methylaminomethyl, 2-methylaminoethyl or 2-hydroxyethylaminomethyl group), the reductive amination of a compound of the Formula I wherein a  $R^6$  group is a group of the formula  $-X^6-R^{15}$  wherein  $R^{15}$  is a formyl or  
10 (2-6C)alkanoyl group.

A suitable reducing agent for the reductive amination reaction is, for example, a hydride reducing agent, for example an alkali metal aluminium hydride such as lithium aluminium hydride or, preferably, an alkali metal borohydride such as sodium borohydride, sodium cyanoborohydride, sodium triethylborohydride, sodium trimethoxyborohydride and  
15 sodium triacetoxyborohydride. The reaction is conveniently performed in a suitable inert solvent or diluent, for example tetrahydrofuran and diethyl ether for the more powerful reducing agents such as lithium aluminium hydride, and, for example, methylene chloride or a protic solvent such as methanol and ethanol for the less powerful reducing agents such as sodium triacetoxyborohydride and sodium cyanoborohydride. The reaction is performed at a  
20 temperature in the range, for example, 10 to 80°C, conveniently at or near ambient temperature.

Compounds of the Formula I wherein a  $R^6$  group is a group of the formula  $-X^6-R^{15}$  wherein  $R^{15}$  is a formyl or (2-6C)alkanoyl group may be obtained by a conventional adaptation of any of the representative process variants (a), (b) or (c) that are described hereinbefore.

- 25 When a pharmaceutically-acceptable salt of a quinoline derivative of the Formula I is required, for example an acid-addition salt, it may be obtained by, for example, reaction of said quinoline derivative with a suitable acid.

When a pharmaceutically-acceptable pro-drug of a quinoline derivative of the Formula I is required, it may be obtained using a conventional procedure. For example, an  
30 *in vivo* cleavable ester of a quinoline derivative of the Formula I may be obtained by, for example, reaction of a compound of the Formula I containing a carboxy group with a pharmaceutically-acceptable alcohol or by reaction of a compound of the Formula I containing

- 65 -

a hydroxy group with a pharmaceutically-acceptable carboxylic acid. For example, an *in vivo* cleavable amide of a quinoline derivative of the Formula I may be obtained by, for example, reaction of a compound of the Formula I containing a carboxy group with a pharmaceutically-acceptable amine or by reaction of a compound of the Formula I containing an amino group with a pharmaceutically-acceptable carboxylic acid.

Many of the intermediates defined herein are novel and these are provided as a further feature of the invention. For example, many compounds of the Formulae III, VI and VII are novel compounds.

#### Biological Assays

The following assays can be used to measure the effects of the compounds of the present invention as inhibitors of PDGFR $\alpha$ , PDGFR $\beta$  and KDR tyrosine kinase enzymes, as inhibitors *in vitro* of the phosphorylation of PDGFR expressed on MG63 osteosarcoma cells, as inhibitors *in vitro* of the proliferation of MG63 osteosarcoma cells, as inhibitors *in vitro* of the proliferation of human umbilical vein endothelial cells (HUVECs), and as inhibitors *in vivo* of the growth in nude mice of xenografts of human tumour tissue such as CaLu-6 and Colo205.

##### (a) In Vitro Enzyme Assays

The ability of test compounds to inhibit the phosphorylation of a tyrosine containing polypeptide substrate by the tyrosine kinase enzymes PDGFR $\alpha$ , PDGFR $\beta$  and KDR was assessed using conventional ELISA assays.

DNA encoding the PDGFR $\alpha$ , PDGFR $\beta$  or KDR receptor cytoplasmic domains may be obtained by total gene synthesis (International Biotechnology Lab., 1987, 5(3), 19-25) or by cloning. The DNA fragments may be expressed in a suitable expression system to obtain polypeptide with tyrosine kinase activity. For example, PDGFR $\alpha$ , PDGFR $\beta$  and KDR receptor cytoplasmic domains, obtained by expression of recombinant protein in insect cells, can be shown to display intrinsic tyrosine kinase activity. In the case of the VEGF receptor KDR (Genbank Accession No. L04947), a DNA fragment encoding most of the cytoplasmic domain, commencing with methionine 806 and including the termination codon may be cloned into a baculovirus transplacement vector [for example pAcYM1 (see The Baculovirus Expression System: A Laboratory Guide, L.A. King and R. D. Possee, Chapman and Hall, 1992) or pAc360 or pBlueBacHis (available from Invitrogen Corporation)]. This recombinant construct may be co-transfected into insect cells [for example *Spodoptera frugiperda* 21(Sf21) or *Spodoptera frugiperda* 9(Sf9)] with viral DNA (for example Pharmingen BaculoGold) to

- 66 -

prepare recombinant baculovirus. Details of the methods for the assembly of recombinant DNA molecules and the preparation and use of recombinant baculovirus can be found in standard texts, for example Sambrook *et al.*, 1989, Molecular cloning - A Laboratory Manual, 2nd edition, Cold Spring Harbour Laboratory Press and O'Reilly *et al.*, 1992, Baculovirus Expression Vectors - A Laboratory Manual, W. H. Freeman and Co, New York).

For expression, Sf9 cells were infected with plaque-pure KDR recombinant virus and harvested 48 hours later. Harvested cells were washed with ice cold phosphate buffered saline solution (PBS) containing 10 mM sodium phosphate pH7.4 buffer, 138 mM sodium chloride and 2.7 mM potassium chloride) and resuspended in ice cold cell diluent comprising 20 mM Hepes pH7.5 buffer, 150 mM sodium chloride, 10% v/v glycerol, 1% v/v Triton X100, 1.5 mM magnesium chloride, 1 mM ethylene glycol-bis( $\beta$ aminoethyl ether) *N,N,N',N'*-tetraacetic acid (EGTA) and 1 mM PMSF (phenylmethylsulphonyl fluoride) [the PMSF is added just before use from a freshly-prepared 100 mM solution in methanol] using 1 ml cell diluent per 10 million cells. The suspension was centrifuged for 10 minutes at 13,000 rpm at 4°C. The supernatant (stock enzyme solution) was removed and stored in aliquots at -70°C.

A substrate solution [100  $\mu$ l of a 2  $\mu$ g/ml solution of the poly-amino acid Poly(Glu, Ala, Tyr) 6:3:1 (Sigma-Aldrich Company Ltd., Poole, Dorset; Catalogue No. P3899) in phosphate buffered saline (PBS)] was added to each well of a number of Nunc 96-well MaxiSorp immunoplates (Nunc, Roskilde, Denmark; Catalogue No. 439454) and the plates were sealed and stored at 4°C for 16 hours. The excess of substrate solution was discarded and the wells were washed in turn with PBS containing 0.05% v/v Tween 20 (PBST; 300  $\mu$ l/well) and twice with Hepes pH7.4 buffer (50 mM, 300  $\mu$ l/well) before being blotted dry.

Each test compound was dissolved in DMSO and diluted with a 10% solution of DMSO in distilled water to give a series of dilutions (from 40  $\mu$ M to 0.0012  $\mu$ M). Aliquots (25  $\mu$ l) of each dilution of test compound were transferred to wells in the washed assay plates. "Maximum" control wells contained diluted DMSO instead of compound. Aliquots (25  $\mu$ l) of an aqueous manganese chloride solution (40 mM) containing adenosine-5'-triphosphate (ATP) was added to all test wells except the "blank" control wells which contained magnesium chloride without ATP. For PDGFR $\alpha$  enzyme, an ATP concentration of 14 $\mu$ M was used; for PDGFR $\beta$  enzyme, an ATP concentration of 2.8 $\mu$ M was used and for KDR enzyme, an ATP concentration of 8 $\mu$ M was used.

- 67 -

Active human PDGFR $\alpha$  and PDGFR $\beta$  recombinant enzyme that had been expressed in Sf9 insect cells was obtained from Upstate Biotechnology Inc., Milton Keynes, UK (product 14-467 for PDGFR $\alpha$ , product 14-463 for PDGFR $\beta$ ). Active human KDR recombinant enzyme was expressed in Sf9 insect cells as described above.

5 Each kinase enzyme was diluted immediately prior to use with an enzyme diluent comprising 100 mM Hepes pH7.4 buffer, 0.1 mM sodium orthovanadate, 0.1% Triton X-100 and 0.2 mM dithiothreitol. Aliquots (50  $\mu$ l) of freshly diluted enzyme were added to each well and the plates were agitated at ambient temperature for 20 minutes. The solution in each well was discarded and the wells were washed twice with PBST. Mouse IgG anti-phosphotyrosine  
10 antibody (Upstate Biotechnology Inc.; product 05-321; 100  $\mu$ l) was diluted by a factor of 1:3667 with PBST containing 0.5% w/v bovine serum albumin (BSA) and aliquots were added to each well. The plates were agitated at ambient temperature for 1.5 hours. The supernatant liquid was discarded and each well was washed with PBST (x2). Horse radish peroxidase (HRP)-linked sheep anti-mouse Ig antibody (Amersham Pharmacia Biotech, Chalfont St Giles,  
15 Buckinghamshire, UK; Catalogue No. NXA 931; 100  $\mu$ l) was diluted by a factor of 1:550 with PBST containing 0.5% w/v BSA and added to each well. The plates were agitated at ambient temperature for 1.5 hours. The supernatant liquid was discarded and the wells were washed with PBST (x2). A sodium perborate (PCSB) capsule (Sigma-Aldrich Company Ltd., Poole, Dorset, UK; Catalogue No. P4922) was dissolved in distilled water (100 ml) to provide  
20 phosphate-citrate pH5 buffer (50 mM) containing 0.03% sodium perborate. An aliquot (50 ml) of this buffer was mixed with a 50 mg tablet of 2,2'-azinobis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS; Roche Diagnostics Ltd., Lewes, East Sussex, UK; Catalogue No. 1204 521). An aliquot (100  $\mu$ l) of the resultant solution was added to each well. The plates were agitated at ambient temperature for about 20 minutes until the optical density value  
25 of the "maximum" control wells, as measured at 405nm using a plate reading spectrophotometer, was approximately 1.0. "Blank" (no ATP) and "maximum" (no compound) control values were used to determine the dilution range of test compound that gave 50% inhibition of enzyme activity.

(b) *In Vitro* phospho-Tyr751 PDGFR $\beta$  ELISA Assay

30 This assay uses a conventional ELISA method to determine the ability of test compounds to inhibit phosphorylation of tyrosine in PDGFR $\beta$ .

- 68 -

An MG63 osteosarcoma cell line [American Type Culture Collection (ATCC) CCL 1427] was routinely maintained at 37°C with 7.5% CO<sub>2</sub> in Dulbecco's modified Eagle's growth medium (DMEM; Sigma-Aldrich; Catalogue No. D6546) containing 10% foetal calf serum (FCS; Sigma-Aldrich; Catalogue No. F7524) and 2mM L-glutamine (Invitrogen Ltd.,  
5 Paisley, UK; Catalogue No. 25030-024).

For the assay, the cells were detached from the culture flask using a trypsin/ethylenediaminetetraacetic acid (EDTA) mixture (Invitrogen Ltd.; Catalogue No. 15400-054) and resuspended in test media comprising DMEM without phenol red (Sigma-Aldrich; Catalogue No. D5921) containing 1% charcoal-stripped foetal calf serum (FCS)  
10 (Sigma-Aldrich; Catalogue No. F7524, stripped by incubation with dextran-coated activated charcoal at 55°C for 30 minutes with continuous stirring followed by removal of the charcoal by centrifugation and filter sterilisation) and 2 mM L-glutamine (Invitrogen Ltd., Catalogue No. 25030-024) to give 6x10<sup>4</sup> cells per ml. Aliquots (100 µl) were seeded into each of the wells of columns 2-12 (excluding column 1) and rows B-G (excluding rows A and H) of a  
15 clear 96 well tissue culture plate (Corning Life Sciences, Koolhovenlaan, The Netherlands; Catalogue No. 3595) to give a density of about 6000 cells per well. Aliquots (100 µl) of culture media were placed in the outer wells to minimise edge effects. The cells were incubated overnight at 37°C with 7.5% CO<sub>2</sub> to allow the cells to adhere to the wells.

Test compounds were prepared as 10 mM stock solutions in DMSO and serially diluted  
20 as required with test media to give a range of concentrations. Aliquots (50 µl) of each compound concentration were added to the cells in each well. Control cells received a dilution of DMSO only. The cells were incubated for 90 minutes at 37°C with 7.5% CO<sub>2</sub>.

The resultant cells were stimulated with PDGF<sub>BB</sub> using the following procedure. A lyophilised powder of PDGF<sub>BB</sub>, (Sigma-Aldrich; Catalogue No. P4306) was mixed with  
25 4 mM aqueous hydrochloric acid containing 0.1% filter-sterilised BSA to provide a stock solution of 10 µg/ml of PDGF<sub>BB</sub>. A dilution of this stock solution into test medium provided a 200 ng/ml PDGF<sub>BB</sub> solution. Aliquots thereof (50 µl) were added to compound treated cells and to one set of control wells to give the "maximum" control. The "minimum" controls received media only. The cells were incubated at 37°C with 7.5% CO<sub>2</sub> for 5 minutes. The  
30 solution from the wells was removed and the cells were lysed by the addition of 120 µl/well of RIPA buffer comprising 60 mM *tris*(hydroxymethyl)aminomethane hydrochloride (Tris-HCl), 150 mM sodium chloride, 1 mM EDTA, 1% v/v Igepal CA-630, 0.25% sodium deoxycholate,

1% v/v phosphatase inhibitor cocktail 1 P2850, 1% phosphatase inhibitor cocktail 2 P5726 and 0.5% v/v protease inhibitor cocktail P8340 (all chemicals and inhibitor cocktails were obtainable from the Sigma-Aldrich Company Ltd.). The resultant tissue culture plates were shaken for 5 minutes at ambient temperature to ensure full lysis and then frozen at -20°C until  
5 required.

MaxiSorp ELISA plates (Nunc; Catalogue No. 439454) were coated with PDGF $\beta$  antibody (R&D Systems, Abingdon, Oxfordshire, UK; Catalogue No. AF385 comprising lyophilised antibody made up with 100  $\mu$ l PBS to a final concentration of 100  $\mu$ l/ml). The antibody was diluted at 1:40 into carbonate-bicarbonate buffer (Sigma-Aldrich; Catalogue  
10 No. C3041; one capsule dissolved in 100 ml of distilled water) to give a 2.5  $\mu$ g/ml solution. Aliquots (100  $\mu$ l) were added to each well and the plates were placed at 4°C for 16 hours. The wells were washed 5 times (1 minute soak each time) with 300  $\mu$ l per well of PBST. The wells were treated with 50  $\mu$ l of 3% BSA in PBST at ambient temperature for 1 hour and subsequently washed twice with 300  $\mu$ l per well of PBST.

15 The tissue culture plates with frozen cell lysate were allowed to warm to 0°C. Aliquots (50  $\mu$ l) of the MG63 cell lysate were added to the ELISA plates. Each sample was duplicated on separate plates. The ELISA plates were agitated at ambient temperature for 2 hours. The wells were washed twice with 300  $\mu$ l per well of PBST. A 1:1000 dilution of both total PDGFR $\beta$  antibody (Upstate Biotechnology Inc.; Catalogue No. 06-498) and phospho PDGFR $\beta$   
20 antibody (Cell Signaling Technology, Beverly, MA, USA; Catalogue No. 3161) was made into 1% BSA in PBST. Aliquots (50  $\mu$ l) of the antibody solutions were added to each of the wells. Plates receiving the total antibody were labelled as 'total antibody control' plates, and plates receiving the phosphospecific antibody were labelled as 'phospho antibody' plates. The plates were agitated at ambient temperature for 1 hour. The plates were washed twice with  
25 300  $\mu$ l per well of PBST. A 1:2000 dilution of anti-rabbit horseradish peroxidase conjugated secondary antibody (Cell Signaling Technology; Catalogue No. 7074) was made into 1% BSA in PBST. Aliquots (50  $\mu$ l) of the resultant dilution were added to each well and the plates were agitated at ambient temperature for 1 hour. The plates were washed 5 times with 300  $\mu$ l per well of PBST. Chemiluminescent substrate was made up according to manufacturers  
30 instructions (Pierce Biotechnology Inc., Rockford IL, USA; Catalogue No. 34080). Aliquots (50  $\mu$ l) of chemiluminescent substrate solution were added to each of the wells, the plates were agitated for 2 minutes and luminescence was read on a SpectraFluor Plus plate reader

- 70 -

(Tecan UK Ltd., Reading, Berkshire, UK). Analysis for each of the compounds was completed by determining a ratio of the 'phospho antibody' plate reading to the 'total antibody' plate reading for each test sample and these ratios were plotted to determine the IC<sub>50</sub> value of each test compound.

5 (c) In Vitro MG63 Osteosarcoma Proliferation Assay

This assay determined the ability of a test compound to inhibit the proliferation of MG63 osteosarcoma cells (ATCC CCL 1427).

MG63 cells were seeded at  $1.5 \times 10^3$  cells per well into 96-well clear tissue culture-treated assay plates (Corning Life Sciences; Catalogue No. 3595) to which had been  
10 added 60  $\mu$ l per well of test medium comprising DMEM without phenol red, 1% charcoal-stripped FCS and 2 mM glutamine and the cells were incubated overnight at 37°C with 7.5% CO<sub>2</sub>.

Test compounds were solubilised in DMSO to provide a 10 mM stock solution. Aliquots of the stock solution were diluted with the test medium described above and 20  $\mu$ l  
15 aliquots of each dilution were added to appropriate wells. Serial dilutions were made to give a range of test concentrations. Control wells to which DMSO solution only was added were included on each plate. Each plate was duplicated. A lyophilised powder of PDGF<sub>BB</sub> was mixed with 4 mM aqueous hydrochloric acid containing 0.1% filter-sterilised BSA to provide a stock solution of 10  $\mu$ g/ml of PDGF<sub>BB</sub>. A dilution of this stock solution into test medium  
20 provided a 250 ng/ml PDGF<sub>BB</sub> solution. Aliquots (20  $\mu$ l) thereof were added to one set of control wells to give the "maximum" control. Aliquots (20  $\mu$ l) thereof were added to one set of the duplicate compound-treated plates and these were denoted as the "PDGF<sub>BB</sub> stimulated" plates. The second set of duplicate compound-treated plates received media only and these were denoted as the "basal" plates. The "minimum" controls received media only. The plates  
25 were incubated at 37°C with 7.5% CO<sub>2</sub> for 72 hours.

BrdU labelling reagent (Roche Diagnostics Ltd., Lewes, East Sussex, UK; Catalogue No. 647 229) was diluted by a factor of 1:100 in DMEM medium containing 1% charcoal stripped FCS and aliquots (10  $\mu$ l) were added to each well to give a final concentration of 10  $\mu$ M. The plates were incubated at 37°C for 2 hours. The medium was  
30 decanted. A denaturing solution (FixDenat solution, Roche Diagnostics Ltd.; Catalogue No. 647 229; 200  $\mu$ l) was added to each well and the plates were agitated at ambient temperature for 30 minutes. The supernatant was decanted and the wells were washed with

- 71 -

PBS (200 µl per well). Anti-BrdU-Peroxidase solution (Roche Diagnostics Ltd.; Catalogue No. 647 229) was diluted by a factor of 1:100 in antibody diluent (Roche Diagnostics Ltd., Catalogue No. 647 229) and 100 µl of the resultant solution was added to each well. The plates were agitated at ambient temperature for 90 minutes. The wells were washed with PBS (x3; 300 µl) to ensure removal of non-bound antibody conjugate. The plates were blotted dry and tetramethylbenzidine substrate solution (Roche Diagnostics Ltd.; Catalogue No. 647 229; 100 µl) was added to each well. The plates were gently agitated on a plate shaker while the colour developed during a 10 to 20 minute period. Aqueous sulphuric acid (1M; 50 µl) was added to the appropriate wells to stop any further reaction and the absorbance of the wells was measured at 450nm. The extent of inhibition of cellular proliferation at a range of concentrations of each test compound was determined and an anti-proliferative IC<sub>50</sub> value was derived.

(d) In Vitro HUVEC Proliferation Assay

This assay determines the ability of a test compound to inhibit the growth factor-stimulated proliferation of human umbilical vein endothelial cells (HUVECs).

HUVECs were isolated in MCDB 131 (Gibco BRL) and 7.5% v/v foetal calf serum (FCS) and were plated out (at passage 2 to 8) in a mixture of MCDB 131, 2% v/v FCS, 3 µg/ml heparin and 1 µg/ml hydrocortisone, at a concentration of 1000 cells/well in 96 well plates. After a minimum of 4 hours, the cells were dosed with the appropriate growth factor (for example VEGF) and with the test compound. The cultures were incubated for 4 days at 37°C under 7.5% CO<sub>2</sub>. On day 4, the cell cultures were pulsed with 1 µCi/well of tritiated-thymidine (Amersham product TRA 61) and incubated for 4 hours. The cells were harvested using a 96-well plate harvester (Tomtek) and assayed for incorporation of tritium with a Beta plate counter. Incorporation of radioactivity into cells, expressed as counts per minute (cpm), was used to measure inhibition of growth factor-stimulated cell proliferation by each test compound.

(e) In Vivo Solid Tumour Disease Model

This test measures the capacity of compounds to inhibit solid tumour growth.

CaLu-6 tumour xenografts were established in the flank of female athymic Swiss *nu/nu* mice, by subcutaneous injection of 1x10<sup>6</sup> CaLu-6 cells/mouse in 100 µl of a 50% (v/v) solution of Matrigel in serum free culture medium. Ten days after cellular implant, mice were allocated



- 72 -

to groups of 8-10 animals having comparable group mean tumour volumes. Tumours were measured using vernier calipers and volumes were calculated using the formula

$$(l \times w) \times \sqrt{(l \times w)} \times (\pi/6)$$

where  $l$  is the longest diameter and  $w$  the diameter perpendicular to the longest. Test

- 5 compounds were administered orally once daily for a minimum of 21 days, and control animals received compound diluent only. Tumours were measured twice weekly. The level of growth inhibition was calculated by comparison of the mean tumour volume of the control group versus the treatment group using a Student's T test and/or a Mann-Whitney Rank Sum Test.

Although the pharmacological properties of the compounds of the Formula I vary with  
10 structural change as expected, in general activity possessed by compounds of the Formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b), (c), (d) and (e) :-

- Test (a):-  $IC_{50}$  versus PDGFR $\alpha$  tyrosine kinase in the range, for example,  
0.1 nM - 5  $\mu$ M;  
15  $IC_{50}$  versus PDGFR $\beta$  tyrosine kinase in the range, for example,  
0.1 nM - 5  $\mu$ M;  
Test (b):-  $IC_{50}$  versus phospho-Tyr751 PDGFR $\beta$  in the range, for example,  
0.1 nM - 1  $\mu$ M;  
Test (c):-  $IC_{50}$  versus MG63 osteosarcoma proliferation in the range, for example,  
20 1 nM - 5  $\mu$ M;  
Test (d):-  $IC_{50}$  versus VEGF driven HUVEC proliferation in the range, for  
example, 1  $\mu$ M - 25  $\mu$ M;  
Test (e):- xenograft activity in the range, for example, 1-200 mg/kg/day.

For example, the quinoline compound disclosed within Example 1 possesses activity in  
25 Test (a) with an  $IC_{50}$  versus PDGFR $\alpha$  tyrosine kinase of approximately 0.5  $\mu$ M, with an  
 $IC_{50}$  versus PDGFR $\beta$  tyrosine kinase of approximately 0.1  $\mu$ M, and with an  $IC_{50}$  versus KDR  
tyrosine kinase of approximately 6  $\mu$ M; and activity in Test (b) with an  $IC_{50}$  versus  
phospho-Tyr751 PDGFR $\beta$  of approximately 2 nM.

For example, the quinoline compound disclosed as Compound No. 7 within Example 2  
30 possesses activity in Test (a) with an  $IC_{50}$  versus PDGFR $\alpha$  tyrosine kinase of approximately  
0.1  $\mu$ M, with an  $IC_{50}$  versus PDGFR $\beta$  tyrosine kinase of approximately 0.02  $\mu$ M, and with an

- 73 -

IC<sub>50</sub> versus KDR tyrosine kinase of approximately 1.3  $\mu$ M; and activity in Test (b) with an IC<sub>50</sub> versus phospho-Tyr751 PDGFR $\beta$  of less than 1 nM.

For example, the quinoline compound disclosed as Compound No. 8 within Example 3 possesses activity in Test (a) with an IC<sub>50</sub> versus KDR tyrosine kinase of approximately 3  $\mu$ M;  
5 and activity in Test (b) with an IC<sub>50</sub> versus phospho-Tyr751 PDGFR $\beta$  of approximately 10 nM.

No untoward toxicological effects are expected when a compound of Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore is administered at the dosage ranges defined hereinafter.

According to a further aspect of the invention there is provided a pharmaceutical  
10 composition which comprises a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible  
15 powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intraperitoneal or intramuscular dosing or as a  
20 suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

25 The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 1 mg to 1 g of active agent (more suitably from 1 to 250 mg, for example from 1 to 100 mg) compounded with an appropriate and  
30 convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the

- 74 -

Formula I will naturally vary according to the nature and severity of the disease state, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 1 mg/kg to 100 mg/kg body weight is received, given if required in divided doses. In general, lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 1 mg/kg to 25 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 1 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 10 mg to 0.5 g of a compound of this invention.

As stated above, antagonism of the activity of PDGF receptor kinases, particularly inhibition of the PDGF $\alpha$  and/or PDGF $\beta$  receptor tyrosine kinases, is expected to be beneficial in the treatment of a number of cell proliferative disorders such as cancer, especially in inhibiting tumour growth and metastasis and in inhibiting the progression of leukaemia.

We have now found that the novel quinoline derivatives described herein possess potent activity against cell proliferative disorders. It is believed that the compounds provide a useful treatment of cell proliferative disorders, for example to provide an anti-tumour effect, by way of a contribution from inhibition of PDGF receptor tyrosine kinases. In addition, as stated hereinbefore, PDGF is involved in angiogenesis, the process of forming new blood vessels that is critical for continuing tumour growth. It is therefore believed that the compounds of the present invention are expected to be beneficial in the treatment of a number of disease states that are associated with angiogenesis and/or increased vascular permeability such as cancer, especially in inhibiting the development of tumours.

According to this further aspect of the invention there is provided a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, as defined hereinbefore for use as a medicament in a warm-blooded animal such as man.

According to a further aspect of the invention, there is provided a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, as defined hereinbefore for use in the treatment (or prophylaxis) of cell proliferative disorders or in the

treatment (or prophylaxis) of disease states associated with angiogenesis and/or vascular permeability.

According to a further aspect of the invention, there is provided the use of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt, solvate or  
5 pro-drug thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment (or prophylaxis) of cell proliferative disorders or in the treatment (or prophylaxis) of disease states associated with angiogenesis and/or vascular permeability.

According to this aspect of the invention there is also provided a method for the treatment (or prophylaxis) of cell proliferative disorders in a warm-blooded animal in need of  
10 such treatment (or prophylaxis) or for the treatment (or prophylaxis) of disease states associated with angiogenesis and/or vascular permeability in a warm-blooded animal in need of such treatment (or prophylaxis) which comprises administering to said animal an effective amount of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, as defined hereinbefore.

15 Suitable cell proliferative disorders include neoplastic disorders, for example, cancers of the lung (non-small cell lung cancer, small cell lung cancer and bronchioalveolar cancer), gastrointestinal (such as colon, rectal and stomach tumours), prostate, breast, kidney, liver, brain (such as glioblastoma), bile duct, bone, bladder, head and neck, oesophagus, ovary, pancreas, testes, thyroid, cervix and vulva and skin (such as dermatofibrosarcoma  
20 protruberans) and in leukaemias and lymphomas such as chronic myelogenous leukaemia (CML), chronic myelomonocytic leukaemia (CMML), acute lymphocytic leukaemia (ALL), chronic neutrophilic leukaemia (CNL), acute myelogenous leukaemia (AML) and multiple myeloma.

According to this aspect of the invention there is also provided a method for treating  
25 cell proliferative disorders (such as solid tumour disease) in a warm-blooded animal in need of such treatment which comprises administering to said animal an effective amount of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, as defined hereinbefore.

Other suitable cell proliferative disorders include non-malignant disorders such as  
30 blood vessel disease (for example atherosclerosis and restenosis, for example in the process of restenosis subsequent to balloon angioplasty and heart arterial by-pass surgery), fibrotic diseases (for example kidney fibrosis, hepatic cirrhosis, lung fibrosis and multicystic renal dysplasia), glomerulonephritis, benign prostatic hypertrophy, inflammatory diseases (for

- 76 -

example rheumatoid arthritis and inflammatory bowel disease), multiple sclerosis, psoriasis, hypersensitivity reactions of the skin, allergic asthma, insulin-dependent diabetes, diabetic retinopathy and diabetic nephropathy.

Suitable disease states associated with angiogenesis and/or vascular permeability include, for example, the undesirable or pathological angiogenesis seen in diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma.

According to a further aspect of the invention there is provided a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, as defined hereinbefore for use in the treatment (or prevention) of those tumours which are sensitive to inhibition of PDGF receptor enzymes (such as PDGF $\alpha$  and/or PDGF $\beta$  receptor tyrosine kinase) that are involved in the signal transduction steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells.

According to a further feature of this aspect of the invention there is provided the use of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment (or prevention) of those tumours which are sensitive to inhibition of PDGF receptor enzymes (such as PDGF $\alpha$  and/or PDGF $\beta$  receptor tyrosine kinase) that are involved in the signal transduction steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the treatment (or prevention) of a warm-blooded animal having tumours which are sensitive to inhibition of PDGF receptor enzymes (such as PDGF $\alpha$  and/or PDGF $\beta$  receptor tyrosine kinase) that are involved in the signal transduction steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells which comprises administering to said animal an effective amount of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, as defined hereinbefore for use in providing a PDGF receptor enzyme inhibitory effect (such as a PDGF $\alpha$  and/or PDGF $\beta$  receptor tyrosine kinase inhibitory effect).

According to a further feature of this aspect of the invention there is provided the use of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt, solvate or pro-

- 77 -

drug thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a PDGF receptor enzyme inhibitory effect (such as a PDGF $\alpha$  and/or PDGF $\beta$  receptor tyrosine kinase inhibitory effect).

According to a further aspect of the invention there is also provided a method for  
5 inhibiting a PDGF receptor enzyme (such as the PDGF $\alpha$  and/or PDGF $\beta$  receptor tyrosine kinase) which comprises administering an effective amount of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, as defined hereinbefore.

The anti-cancer treatment defined hereinbefore may be applied as a sole therapy or may  
10 involve, in addition to the quinazoline derivative of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

- (i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin,  
15 cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example  
20 vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);
- (ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide,  
25 flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuporelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 $\alpha$ -reductase such as finasteride;
- (iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-chloro-  
30 2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341) and N-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-

- 78 -

4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; *J. Med. Chem.*, 2004, **47**, 6658-6661), and metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor  
5 antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin™] and the anti-erbB1 antibody cetuximab [C225]); such inhibitors also include, for example, tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839),  
10 *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033) and erbB2 tyrosine kinase inhibitors such as lapatinib), inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as  
15 farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)) and inhibitors of cell signalling through MEK, AKT and/or PI3K kinases;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and VEGF receptor tyrosine kinase inhibitors such as  
20 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-ylloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (sunitinib; WO 01/60814), and compounds that work by other mechanisms (for example linomide, inhibitors of integrin  $\alpha v \beta 3$  function  
25 and angiostatin)];

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above,  
30 such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug

- 79 -

therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to  
5 increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

10 Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

According to this aspect of the invention there is provided a pharmaceutical product  
15 comprising a quinoline derivative of the formula I as defined hereinbefore and an additional anti-tumour agent as defined hereinbefore for the conjoint treatment of cancer.

Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of PDGF receptor tyrosine kinase enzymes. Thus, they are useful as  
20 pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

The invention will now be illustrated in the following Examples in which, generally :

- (i) operations were carried out at ambient temperature, *i.e.* in the range 17 to 25°C and under an atmosphere of an inert gas such as nitrogen or argon unless otherwise stated;
- 25 (ii) in general, the course of reactions was followed by thin layer chromatography (TLC) and/or analytical high pressure liquid chromatography (HPLC); the reaction times that are given are not necessarily the minimum attainable;
- (iii) when necessary, organic solutions were dried over anhydrous magnesium sulphate, work-up procedures were carried out after removal of residual solids by filtration,  
30 evaporations were carried out by rotary evaporation *in vacuo*;
- (iv) yields, where present, are not necessarily the maximum attainable, and, when necessary, reactions were repeated if a larger amount of the reaction product was required;



- 80 -

(v) in general, the structures of the end-products of the Formula I were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; electrospray mass spectral data were obtained using a Waters ZMD or Waters ZQ LC/mass spectrometer acquiring both positive and negative ion data, generally, only ions relating to the parent structure are reported;  
5 proton NMR chemical shift values were measured on the delta scale using a Bruker Spectrospin DPX300 spectrometer operating at a field strength of 300 MHz; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad;

(vi) unless stated otherwise compounds containing an asymmetric carbon and/or  
10 sulphur atom were not resolved;

(vii) intermediates were not necessarily fully purified but their structures and purity were assessed by TLC, analytical HPLC, infra-red (IR) and/or NMR analysis;

(viii) unless otherwise stated, column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica  
15 (Art. 9385);

(ix) preparative HPLC was performed on C18 reversed-phase silica, for example on a Waters 'Xterra' preparative reversed-phase column (5 microns silica, 19 mm diameter, 100 mm length) using decreasingly polar mixtures as eluent, for example decreasingly polar mixtures of 1% aqueous acetic acid or 1% aqueous ammonium hydroxide (d=0.88) solution  
20 and acetonitrile;

(x) where certain compounds were obtained as an acid-addition salt, for example a mono-hydrochloride salt or a di-hydrochloride salt, the stoichiometry of the salt was based on the number and nature of the basic groups in the compound; generally, elemental analysis data were not obtained to determine the exact stoichiometry of the salt;

25 (xi) the following abbreviations have been used:-

DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulphoxide
THF	tetrahydrofuran

**Example 1*****N*-(3-fluorophenyl)-2-[4-(6-cyano-7-methoxyquinolin-4-yloxy)pyrazol-1-yl]acetamide**

Diisopropylethylamine (0.054 g) and 2-(7-azabenzotriazol-1-yl)-  
1,1,3,3-tetramethyluronium hexafluorophosphate(V) (0.159 g) were added in turn to a stirred  
5 mixture of 2-[4-(6-cyano-7-methoxyquinolin-4-yloxy)pyrazol-1-yl]acetic acid (0.123 g),  
3-fluoroaniline (0.051 g) and DMF (1 ml) and the resultant mixture was stirred at ambient  
temperature for 16 hours. Water was added and the precipitate was recovered by filtration and  
dried under vacuum. There was thus obtained the title compound (0.136 g); <sup>1</sup>H NMR:  
(DMSO-d<sub>6</sub>) 4.07 (s, 3H), 5.08 (s, 2H), 6.81 (d, 1H), 6.93 (m, 1H), 7.32 (d, 1H), 7.39 (m, 1H),  
10 7.59 (m, 1H), 7.62 (s, 1H), 7.66 (s, 1H), 8.07 (s, 1H), 8.77 (s, 1H), 8.83 (d, 1H), 10.6 (s, 1H);  
Mass Spectrum: M+H<sup>+</sup> 418.

The 2-[4-(6-cyano-7-methoxyquinolin-4-yloxy)pyrazol-1-yl]acetic acid used as a  
starting material was prepared as follows :-

A mixture of 4-(*tert*-butyldimethylsilyloxy)-1*H*-pyrazole (European Patent Application  
15 No. 0921120, pages 34 and 35 thereof; 2.77 g), *tert*-butyl bromoacetate (2.87 g), potassium  
carbonate (3.86 g) and DMF (40 ml) was stirred at ambient temperature for 21 hours. The  
resultant mixture was evaporated and the residue was partitioned between ethyl acetate and  
water. The organic phase was washed with a saturated aqueous sodium chloride solution,  
dried over magnesium sulphate and evaporated. There was thus obtained *tert*-butyl  
20 2-[4-(*tert*-butyldimethylsilyloxy)pyrazol-1-yl]acetate as a pale yellow liquid (4.37 g);  
<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 0.16 (s, 6H), 0.94 (s, 9H), 1.42 (s, 9H), 4.77 (s, 2H), 7.14 (s, 1H), 7.4 (s,  
1H); Mass Spectrum: M+H<sup>+</sup> 313.

Tetra-*n*-butylammonium fluoride (1.1 M in THF; 1.1 ml) and acetic acid (0.144 g) were  
added in turn to a solution of *tert*-butyl 2-[4-(*tert*-butyldimethylsilyloxy)pyrazol-  
25 1-yl]acetate (0.312 g) in THF (2 ml) that had been cooled to 5°C. The resultant mixture was  
stirred at ambient temperature for 1 hour. The reaction mixture was diluted with a saturated  
aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic phase was  
recovered, washed with water, dried over magnesium sulphate and evaporated. The residual  
oil was triturated under diethyl ether. There was thus obtained *tert*-butyl 2-(4-hydroxypyrazol-  
30 1-yl)acetate (0.165 g); <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 1.4 (s, 9H), 4.72 (s, 2H), 7.01 (s, 1H), 7.18 (s,  
1H), 8.42 (s, 1H).

Sodium hydride (60% dispersion in mineral oil, 0.163 g) was added portionwise to a  
stirred mixture of *tert*-butyl 2-(4-hydroxypyrazol-1-yl)acetate (0.733 g) and DMF (15 ml) and

the resultant mixture was stirred at ambient temperature for 30 minutes. 4-Chloro-6-cyano-7-methoxyquinoline (0.808 g; International Patent Application WO 02/12226, Example 1 thereof, which concerns analogous procedures to those described for the starting material in Example 1 of International Patent Application WO 98/13350 but where methanol is used instead of 2-methoxyethanol) was added portionwise and the resultant mixture was stirred at ambient temperature for 1 hour. The mixture was evaporated and the residue was purified by column chromatography on silica using in turn a 1:1 mixture of methylene chloride and diethyl ether and a 10:9:1 mixture of methylene chloride, diethyl ether and methanol as eluents. There was thus obtained *tert*-butyl 2-[4-(6-cyano-7-methoxyquinolin-4-yloxy)pyrazol-1-yl]acetate (1.15 g); <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 1.54 (s, 9H), 4.07 (s, 3H), 4.98 (s, 2H), 6.75 (d, 1H), 7.6 (s, 1H), 7.65 (s, 1H), 8.02 (s, 1H), 8.76 (s, 1H), 8.81 (d, 1H); Mass Spectrum: M+H<sup>+</sup> 381.

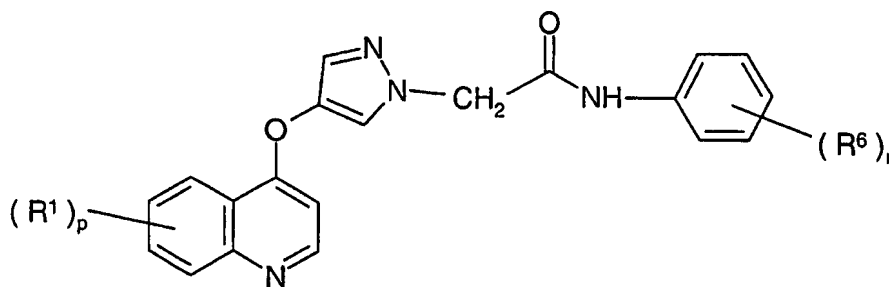
A mixture of a portion (1.28 g) of the material so obtained, trifluoroacetic acid (10 ml), water (0.5 ml) and methylene chloride (2.5 ml) was stirred at ambient temperature for 1 hour. The resultant mixture was evaporated and the residue was triturated under diethyl ether. The resultant precipitate was recovered by filtration, suspended in methylene chloride and treated with diisopropylethylamine (2.5 ml). The resultant solution was evaporated and the residual oil was triturated under a mixture of diethyl ether and ethyl acetate. The solid so obtained was dried under vacuum. There was thus obtained 2-[4-(6-cyano-7-methoxyquinolin-4-yloxy)pyrazol-1-yl]acetic acid (0.802 g); <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 4.07 (s, 3H), 4.98 (s, 2H), 6.77 (d, 1H), 7.61 (s, 1H), 7.64 (s, 1H), 8.02 (s, 1H), 8.76 (s, 1H), 8.81 (d, 1H).

### Example 2

Using an analogous procedure to that described in Example 1, the appropriate 2-(pyrazol-1-yl)acetic acid was reacted with the appropriate aniline to give the compounds described in Table I. Unless otherwise stated, each aniline was a commercially available material.

- 83 -

Table I



No. & Note	(R <sup>1</sup> ) <sub>p</sub>	(R <sup>6</sup> ) <sub>r</sub>
[1]	6-cyano-7-methoxy	3-methoxy
[2]	6-cyano-7-methoxy	4-methoxy
[3]	6-cyano-7-methoxy	2,4-dimethoxy
[4]	6,7-dimethoxy	3-methoxy
[5]	6-cyano-7-methoxy	3-dimethylamino
[6]	6-cyano-7-methoxy	4-dimethylamino
[7]	6,7-dimethoxy	3-dimethylamino
[8]	6-cyano-7-methoxy	2,3-methylenedioxy
[9]	6-cyano-7-methoxy	3,4-methylenedioxy
[10]	6-cyano-7-methoxy	3-hydroxymethyl
[11]	6-cyano-7-methoxy	3-dimethylaminomethyl
[12]	6-cyano-7-methoxy	4-dimethylaminomethyl
[13]	6-cyano-7-methoxy	3-(2-dimethylaminoethyl)

5 **Notes** The products gave the characterising data shown below.

- [1] **<sup>1</sup>H NMR Spectrum:** (DMSO-d<sub>6</sub>) 3.74 (s, 3H), 4.08 (s, 3H), 5.06 (s, 2H), 6.68 (m, 1H), 6.83 (d, 1H), 7.13 (d, 1H), 7.25 (m, 1H), 7.31 (m, 1H), 7.62 (s, 1H), 7.66 (s, 1H), 8.07 (s, 1H), 8.78 (s, 1H), 8.83 (d, 1H), 10.35 (s, 1H); **Mass Spectrum:** M+H<sup>+</sup> 430.
- [2] **<sup>1</sup>H NMR Spectrum:** (DMSO-d<sub>6</sub>) 3.73 (s, 3H), 4.08 (s, 3H), 5.03 (s, 2H), 6.84 (d, 1H), 6.91 (d, 2H), 7.51 (d, 2H), 7.62 (s, 1H), 7.66 (s, 1H), 8.07 (s, 1H), 8.8 (s, 1H), 8.85 (d, 1H), 10.22 (s, 1H); **Mass Spectrum:** M+H<sup>+</sup> 430.
- [3] **<sup>1</sup>H NMR Spectrum:** (DMSO-d<sub>6</sub>) 3.76 (s, 3H), 3.84 (s, 3H), 4.08 (s, 3H), 5.06 (s, 2H), 6.50 (m, 1H), 6.64 (d, 1H), 6.86 (d, 1H), 7.62 (s, 1H), 7.68 (s, 1H), 7.78 (d, 1H), 8.07 (s, 1H), 8.82 (s, 1H), 8.86 (d, 1H), 9.37 (s, 1H); **Mass Spectrum:** M+H<sup>+</sup> 460.

- 84 -

[4] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 3.73 (s, 3H), 3.95 (s, 6H), 5.04 (s, 2H), 6.67 (m, 1H), 6.70 (d, 1H), 7.13 (d, 1H), 7.24 (m, 1H), 7.31 (m, 1H), 7.39 (s, 1H), 7.51 (s, 1H), 7.62 (s, 1H), 8.02 (s, 1H), 8.53 (s, 1H), 10.34 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 435.

The 2-[4-(6,7-dimethoxyquinolin-4-yloxy)pyrazol-1-yl]acetic acid used as a starting  
5 material was prepared as follows :-

A mixture of 4-chloro-6,7-dimethoxyquinoline (1.4 g; International Patent Application WO 98/13350, Example 2 thereof), *tert*-butyl 2-(4-hydroxypyrazol-1-yl)acetate (1.54 g), potassium carbonate (1.3 g) and DMF (25 ml) was stirred and heated to 120°C for 18 hours. The resultant mixture was evaporated and the residue was purified by column chromatography  
10 on silica using a solvent gradient from a 3:2 to a 3:7 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained *tert*-butyl 2-[4-(6,7-dimethoxyquinolin-4-yloxy)pyrazol-1-yl]acetate as a solid (0.731 g); <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 1.45 (s, 9H), 3.94 (s, 6H), 4.97 (s, 2H), 6.63 (d, 1H), 7.39 (s, 1H), 7.5 (s, 1H), 7.62 (s, 1H), 7.98 (s, 1H), 8.51 (d, 1H); Mass Spectrum: M+H<sup>+</sup> 386.

15 A mixture of the material so obtained, trifluoroacetic acid (3.5 ml), water (0.5 ml) and methylene chloride (3.5 ml) was stirred at ambient temperature for 4 hours. The resultant mixture was evaporated and the residue was triturated under ethyl acetate. The resultant precipitate was recovered by filtration, suspended in methylene chloride and treated with diisopropylethylamine. The resultant solution was evaporated and the residual oil was  
20 triturated under a mixture of methylene chloride and ethyl acetate. The solid so obtained was dried under vacuum. There was thus obtained 2-[4-(6,7-dimethoxyquinolin-4-yloxy)pyrazol-1-yl]acetic acid (0.573 g); <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 3.94 (s, 6H), 4.97 (s, 2H), 6.66 (d, 1H), 7.39 (s, 1H), 7.5 (s, 1H), 7.6 (s, 1H), 7.98 (s, 1H), 8.51 (d, 1H); Mass Spectrum: M+H<sup>+</sup> 330.

[5] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 2.88 (s, 6H), 4.07 (s, 3H), 5.03 (s, 2H), 6.47 (d, 1H),  
25 6.83 (d, 1H), 6.9 (d, 1H), 7.05 (s, 1H), 7.12 (m, 1H), 7.62 (s, 1H), 7.65 (s, 1H), 8.06 (s, 1H), 8.78 (s, 1H), 8.83 (d, 1H), 10.17 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 443.

[6] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 2.86 (s, 6H), 4.07 (s, 3H), 5.0 (s, 2H), 6.71 (d, 2H), 6.82 (d, 1H), 7.42 (d, 2H), 7.62 (s, 1H), 7.64 (s, 1H), 8.05 (s, 1H), 8.77 (s, 1H), 8.82 (d, 1H), 10.05 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 443.

30 [7] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 2.88 (s, 6H), 3.95 (s, 6H), 5.02 (s, 2H), 6.46 (m, 1H), 6.71 (d, 1H), 6.9 (d, 1H), 7.04 (s, 1H), 7.12 (m, 1H), 7.39 (s, 1H), 7.51 (s, 1H), 7.62 (s, 1H), 8.01 (s, 1H), 8.53 (d, 1H), 10.15 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 448.

- 85 -

[8] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 4.08 (s, 3H), 5.1 (s, 2H), 6.07 (s, 2H), 6.75 (d, 1H), 6.79-6.85 (m, 2H), 7.31 (d, 1H), 7.62 (s, 1H), 7.65 (s, 1H), 8.06 (s, 1H), 8.78 (s, 1H), 8.83 (d, 1H), 10.1 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 444.

[9] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 4.08 (s, 3H), 5.02 (s, 2H), 6.0 (s, 2H), 6.84 (d, 1H), 6.88 (d, 1H), 6.98 (m, 1H), 7.3 (s, 1H), 7.62 (s, 1H), 7.65 (s, 1H), 8.06 (s, 1H), 8.8 (s, 1H), 8.85 (d, 1H), 10.27 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 444.

[10] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 4.08 (s, 3H), 4.48 (d, 2H), 5.06 (s, 2H), 5.22 (t, 1H), 6.81 (d, 1H), 7.02 (d, 1H), 7.28 (m, 1H), 7.49 (d, 1H), 7.58 (s, 1H), 7.62 (s, 1H), 7.65 (s, 1H), 8.07 (s, 1H), 8.77 (s, 1H), 8.83 (d, 1H), 10.34 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 430.

[11] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 2.67 (s, 6H), 4.17 (s, 3H), 4.3 (br s, 2H), 5.17 (s, 2H), 7.21-7.27 (m, 2H), 7.47 (m, 1H), 7.61 (d, 1H), 7.75 (s, 1H), 7.79 (s, 1H), 7.88 (s, 1H), 8.11 (s, 1H), 9.13 (s, 1H), 9.21 (d, 1H), 10.61 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 457.

The 3-dimethylaminomethylaniline used as a starting material was prepared as follows :-

Triethylamine (3.64 g) was added dropwise to a mixture of 3-nitrobenzyl bromide (2.6 g), dimethylamine hydrochloride (1.96 g) and methylene chloride (26 ml) and the resultant mixture was stirred at ambient temperature for 2 hours. The solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulphate and concentrated. There was thus obtained *N,N*-dimethyl-*N*-(3-nitrobenzyl)amine (1.6 g); <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 2.18 (s, 6H), 3.34 (s, 2H), 7.63 (t, 1H), 7.75 (d, 1H), 8.12 (m, 2H); Mass Spectrum: M+H<sup>+</sup> 181.

Raney nickel (0.8 g) was washed twice with ethanol and added to a solution of *N,N*-dimethyl-*N*-(3-nitrobenzyl)amine (1.6 g) in a mixture of methanol (10 ml) and ethanol (50 ml). The mixture was stirred under 1.8 atmospheres pressure of hydrogen at ambient temperature for 1 hour. The reaction mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using a solvent gradient from a 19:1 to a 9:1 mixture of methylene chloride and methanol followed by a 9:1 to a 18:3 mixture of methylene chloride and a 7M methanolic ammonia solution as eluent. There was thus obtained 3-dimethylaminomethylaniline (0.85 g); <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 2.11 (s, 6H), 3.2 (s, 2H), 4.96 (br s, 2H), 6.41 (m, 2H), 6.51 (s, 1H), 6.92 (t, 1H); Mass Spectrum: M+H<sup>+</sup> 151.

[12] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 2.46 (br s, 6H), 3.67-3.99 (m, 2H), 4.07 (s, 3H), 5.08 (s, 2H), 6.81 (d, 1H), 7.36 (br s, 2H), 7.62 (s, 1H), 7.64 (br s, 2H), 7.66 (s, 1H), 8.07 (s, 1H), 8.77 (s, 1H), 8.82 (d, 1H), 10.45 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 457.

The 4-dimethylaminomethylaniline used as a starting material was prepared from 4-nitrobenzyl bromide using analogous procedures to those described in Note [11] above for the preparation of 3-dimethylaminomethylaniline. The desired aniline material gave the following characterising data: <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 2.07 (s, 6H), 3.17 (s, 2H), 4.92 (br s, 2H), 6.49 (m, 2H), 6.89 (m, 2H); Mass Spectrum: M+H<sup>+</sup> 151.

[13] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 2.76 (br s, 6H), 2.91 (t, 2H), 3.1-3.23 (m, 2H), 4.07 (s, 3H), 5.06 (s, 2H), 6.8 (d, 1H), 7.01 (s, 1H), 7.31 (m, 1H), 7.38 (d, 1H), 7.62 (s, 1H), 7.65 (br s, 1H), 7.66 (s, 1H), 8.06 (s, 1H), 8.67 (s, 1H), 8.82 (d, 1H), 10.38 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 471.

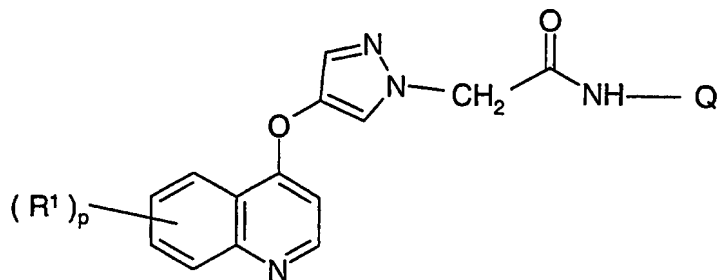
10 The 3-(2-dimethylaminoethyl)aniline used as a starting material was prepared as follows :-

Using analogous procedures to those described in the portion of Note [11] above that is concerned with the preparation of starting materials, 2-(3-nitrophenyl)ethyl bromide was converted into *N,N*-dimethyl-*N*-[2-(3-nitrophenyl)ethyl]amine; <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 2.17 (s, 6H), 2.5 (m, 2H), 2.86 (m, 2H), 7.57 (t, 1H), 7.72 (d, 1H), 8.04 (m, 1H), 8.11 (m, 1H); which in turn was converted into 3-(2-dimethylaminoethyl)aniline; <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 2.15 (s, 6H), 2.38 (m, 2H), 2.51 (m, 2H), 4.91 (br s, 2H), 6.35 (m, 3H), 6.89 (t, 1H); Mass Spectrum: M+H<sup>+</sup> 165.

### 20 Example 3

Using an analogous procedure to that described in Example 1, the appropriate 2-(pyrazol-1-yl)acetic acid was reacted with the appropriate heteroarylamine to give the compounds described in Table II. Unless otherwise stated, each heteroarylamine was a commercially available material.

Table II



No. & Note	(R <sup>1</sup> ) <sub>p</sub>	Q
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- 87 -

[1]	6-cyano-7-methoxy	3-pyridyl
[2]	6-cyano-7-methoxy	6-methoxypyrid-3-yl
[3]	6-cyano-7-methoxy	2,6-dimethoxypyrid-3-yl
[4]	6-cyano-7-methoxy	6-dimethylaminopyrid-3-yl
[5]	6-cyano-7-methoxy	2-dimethylaminopyrid-4-yl
[6]	6,7-dimethoxy	5-methylisoxazol-3-yl
[7]	6-cyano-7-methoxy	1H-indazol-6-yl
[8]	6-cyano-7-methoxy	5-dimethylaminopyrid-2-yl
[9]	6-cyano-7-methoxy	4-dimethylaminopyrid-2-yl

Notes The products gave the characterising data shown below.

[1] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 4.07 (s, 3H), 5.12 (s, 2H), 6.81 (d, 1H), 7.39 (m, 1H), 7.62 (s, 1H), 7.67 (s, 1H), 8.05 (m, 1H), 8.08 (s, 1H), 8.31 (d, 1H), 8.76 (d, 1H), 8.77 (s, 1H), 8.82 (d, 1H), 10.6 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 401.

[2] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 3.84 (s, 3H), 4.07 (s, 3H), 5.06 (s, 2H), 6.81 (d, 1H), 6.84 (d, 1H), 7.62 (s, 1H), 7.66 (s, 1H), 7.91 (m, 1H), 8.07 (s, 1H), 8.37 (d, 1H), 8.77 (s, 1H), 8.82 (d, 1H), 10.39 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 431.

[3] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 3.85 (s, 3H), 3.96 (s, 3H), 4.07 (s, 3H), 5.11 (s, 2H), 6.38 (d, 1H), 6.82 (d, 1H), 7.62 (s, 1H), 7.66 (s, 1H), 8.06 (s, 1H), 8.09 (d, 1H), 8.79 (s, 1H), 8.83 (d, 1H), 9.6 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 461.

[4] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 3.1 (s, 6H), 4.07 (s, 3H), 5.06 (s, 2H), 6.84 (d, 1H), 6.99 (br s, 1H), 7.62 (s, 1H), 7.67 (s, 1H), 7.85 (m, 1H), 8.08 (s, 1H), 8.34 (d, 1H), 8.78 (s, 1H), 8.84 (d, 1H), 10.41 (s, 1H); Mass Spectrum: M-H<sup>-</sup> 442.

The 3-amino-6-dimethylaminopyridine used as a starting material was prepared using a similar procedure to that described in International Patent Application WO 94/04500, example 11 thereof, except that dimethylamine was used in place of trimethylamine.

[5] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 2.99 (s, 6H), 4.07 (s, 3H), 5.08 (s, 2H), 6.74 (m, 1H), 6.81 (d, 1H), 6.94 (s, 1H), 7.62 (s, 1H), 7.66 (s, 1H), 7.98 (d, 1H), 8.06 (s, 1H), 8.77 (s, 1H), 8.83 (d, 1H), 10.47 (br s, 1H); Mass Spectrum: M-H<sup>-</sup> 442.

The 4-amino-2-dimethylaminopyridine used as a starting material was prepared using an analogous procedure to that described in International Patent Application WO 98/02438, page 44 thereof.



- 88 -

[6] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 2.38 (s, 3H), 3.95 (s, 6H), 5.08 (s, 2H), 6.62 (s, 1H), 6.69 (d, 1H), 7.39 (s, 1H), 7.51 (s, 1H), 7.63 (s, 1H), 8.01 (s, 1H), 8.53 (d, 1H), 11.33 (s, 1H);

Mass Spectrum: M+H<sup>+</sup> 410.

[7] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 4.08 (s, 3H), 5.08 (s, 2H), 6.83 (d, 1H), 7.45 (d, 1H), 7.52 (d, 1H), 7.62 (s, 1H), 7.66 (s, 1H), 8.04 (s, 1H), 8.09 (s, 1H), 8.13 (s, 1H), 8.78 (s, 1H), 8.83 (d, 1H), 10.36 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 440.

[8] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 2.9 (s, 6H), 4.07 (s, 3H), 5.08 (s, 2H), 6.81 (d, 1H), 7.22 (m, 1H), 7.62 (s, 1H), 7.64 (s, 1H), 7.87 (m, 2H), 8.05 (s, 1H), 8.77 (s, 1H), 8.81 (d, 1H); Mass Spectrum: M+H<sup>+</sup> 444.

10 The 2-amino-5-dimethylaminopyridine used as a starting material was prepared as follows :-

An aqueous solution of dimethylamine (40%, 11.3 ml) was added to a stirred suspension of 5-bromo-2-nitropyridine (6.1 g) in ethanol (60 ml) and the resultant mixture was heated to reflux for 16 hours. The mixture was cooled to ambient temperature and the solid  
15 was isolated, washed with water and dried under vacuum. There was thus obtained 5-dimethylamino-2-nitropyridine (4 g); <sup>1</sup>H NMR: (CDCl<sub>3</sub>) 3.16 (s, 6H), 6.98 (m, 1H), 7.96 (m, 1H), 8.17 (m, 1H); Mass Spectrum: M+H<sup>+</sup> 168.

A mixture of the material so obtained, platinumium oxide catalyst (0.27 g) ethanol (60 ml) and ethyl acetate (60 ml) was stirred under 5 atmospheres pressure of hydrogen for  
20 3 hours. The catalyst was filtered off and the filtrate was evaporated. There was thus obtained 2-amino-5-dimethylaminopyridine (3 g); <sup>1</sup>H NMR: (CDCl<sub>3</sub>) 2.83 (s, 6H), 4.08 (br s, 2H), 6.49 (m, 1H), 7.08 (m, 1H), 7.67 (m, 1H); Mass Spectrum: M+H<sup>+</sup> 138.

[9] <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 1.9 (s, 3H), 2.95 (s, 6H), 4.07 (s, 3H), 5.11 (s, 2H), 6.41 (d, 1H), 6.82 (d, 1H), 7.4 (br s, 1H), 7.6 (s, 1H), 7.65 (s, 1H), 7.9 (d, 1H), 8.06 (s, 1H),  
25 8.76 (s, 1H), 8.82 (d, 1H), 10.49 (br s, 1H); Mass Spectrum: M+H<sup>+</sup> 444.

The 2-amino-4-dimethylaminopyridine used as a starting material was prepared as follows :-

A mixture of 2-amino-4-chloropyridine (Organic Preparation and Procedure, 1997, 29, 117-122; 0.4 g) and an aqueous solution of dimethylamine (40%, 1.4 ml) was stirred and  
30 heated to 175°C for 35 minutes in a microwave oven. The reaction mixture was cooled to ambient temperature and transferred onto a Waters 'β Basic Hypersil' reversed-phase preparative HPLC column (5 microns silica, 30 mm diameter, 250 mm length) that was eluted with decreasingly polar mixtures of water (containing 0.2% ammonium carbonate) and

acetonitrile as eluent. There was thus obtained the required starting material in 94% yield;

<sup>1</sup>H NMR: (CDCl<sub>3</sub>) 2.95 (s, 6H), 4.19 (br s, 2H), 5.68 (m, 1H), 6.05 (m, 1H), 7.77 (m, 1H);

Mass Spectrum: M+H<sup>+</sup> 138.

#### 5 Example 4

##### ***N*-(4,5-dimethylthiazol-2-yl)-2-[4-(6-cyano-7-methoxyquinolin-4-yloxy)pyrazol-1-yl]acetamide**

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.393 g) was added to a stirred mixture of 2-[4-(6-cyano-7-methoxyquinolin-4-yloxy)pyrazol-1-yl]acetic acid (0.3 g),  
10 2-amino-4,5-dimethylthiazole (0.191 g), 2-hydroxypyridine *N*-oxide (0.228 g), diisopropylethylamine (0.357 ml) and DMF (3 ml) and the resultant mixture was stirred at ambient temperature for 1 hour. Water was added and the precipitate was recovered by filtration, washed with a mixture of DMF and methanol and dried under vacuum. There was thus obtained the title compound (0.2 g); <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 2.17 (s, 3H), 2.25 (s, 3H), 4.08  
15 (s, 3H), 5.15 (s, 2H), 6.82 (s, 1H), 7.62 (s, 1H), 7.67 (s, 1H), 8.07 (s, 1H), 8.77 (s, 1H), 8.83 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 435.

#### Example 5

##### ***N*-[3-(*N*-cyclopropylaminomethyl)-5-methylphenyl]-2-[4-(6-cyano-7-methoxyquinolin-4-yloxy)pyrazol-1-yl]acetamide**

A mixture of *N*-[3-(*N*-*tert*-butoxycarbonyl-*N*-cyclopropylaminomethyl)-5-methylphenyl]-2-[4-(6-cyano-7-methoxyquinolin-4-yloxy)pyrazol-1-yl]acetamide (0.2 g), trifluoroacetic acid (1 ml) and methylene chloride (9 ml) was stirred at ambient temperature for 12 hours. The resultant mixture was evaporated and the residue was purified by column  
25 chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained the title compound (0.1 g); <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 0.24 (m, 2H), 0.34 (m, 2H), 2.26 (s, 3H), 2.4 (m, 1H), 3.66 (d, 2H), 4.07 (s, 3H), 5.01 (s, 2H), 6.84 (m, 2H), 7.31 (m, 2H), 7.61 (m, 2H), 8.02 (s, 1H), 8.72 (s, 1H), 8.81 (d, 1H), 10.1 (br s, 1H); Mass Spectrum: M+H<sup>+</sup> 483.

30 The *N*-[3-(*N*-*tert*-butoxycarbonyl-*N*-cyclopropylaminomethyl)-5-methylphenyl]-2-[4-(6-cyano-7-methoxyquinolin-4-yloxy)pyrazol-1-yl]acetamide used as a starting material was prepared as follows :-

- 90 -

A mixture of 1,3-dimethyl-5-nitrobenzene (15.15 g), *N*-bromosuccinimide (2 g), benzoyl peroxide (0.484 g) and carbon tetrachloride (250 ml) was stirred and heated to reflux. Further portions of *N*-bromosuccinimide (totalling 21 g) were added portionwise during 4 hours to the heated reaction mixture. The mixture was cooled to ambient temperature. Petroleum ether (b.p. 60-80°C) was added. The mixture was filtered and the filtrate was evaporated to give an oil (25 g) which was shown by NMR analysis to be a mixture of 3-methyl-5-nitrobenzyl bromide (76%), unreacted starting material (~ 19%) and 3-bromomethyl-5-nitrobenzyl bromide (~ 15%). This mixture was used in the next step.

Using an analogous procedure to that described in the portion of Note [11] below Table I in Example 2 that is concerned with the preparation of starting materials, 3-methyl-5-nitrobenzyl bromide was reacted with cyclopropylamine to give *N*-cyclopropyl-*N*-(3-methyl-5-nitrobenzyl)amine in 52% yield; <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 0.24 (m, 2H), 0.34 (m, 2H), 2.03 (m, 1H), 2.42 (s, 3H), 2.88 (br s, 1H), 3.8 (s, 2H), 7.6 (s, 1H), 7.92 (s, 1H), 7.99 (s, 1H).

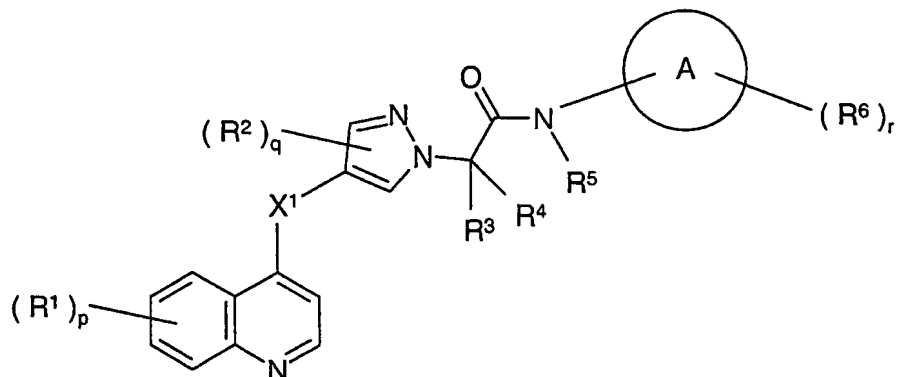
A mixture of *N*-cyclopropyl-*N*-(3-methyl-5-nitrobenzyl)amine (1 g), di-*tert*-butyl dicarbonate (1.2 g) and methylene chloride (20 ml) was stirred at ambient temperature for 4 hours. The solvent was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained *N*-*tert*-butoxycarbonyl-*N*-cyclopropyl-*N*-(3-methyl-5-nitrobenzyl)amine (1.3 g); <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 0.6 (m, 2H), 0.67 (m, 2H), 1.34 (s, 9H), 2.44 (s, 3H), 2.48 (m, 1H), 4.45 (s, 2H), 7.48 (s, 1H), 7.84 (s, 1H), 7.97 (s, 1H).

A mixture of the material so obtained, platinum oxide (0.2 g) and ethyl acetate (25 ml) was stirred under 2 atmospheres pressure of hydrogen for 30 minutes. The catalyst was removed by filtration and the filtrate was evaporated. There was thus obtained 3-(*N*-*tert*-butoxycarbonyl-*N*-cyclopropylaminomethyl)-5-methylaniline (1.1 g); <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 0.56 (m, 2H), 0.63 (m, 2H), 1.4 (s, 9H), 2.12 (s, 3H), 2.37 (m, 1H), 4.16 (s, 2H), 4.95 (s, 2H), 6.16 (s, 1H), 6.21 (s, 1H), 6.24 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 277.

Using an analogous procedure to that described in Example 4, 2-[4-(6-cyano-7-methoxyquinolin-4-yloxy)pyrazol-1-yl]acetic acid was reacted with 3-(*N*-*tert*-butoxycarbonyl-*N*-cyclopropylaminomethyl)-5-methylaniline. The material so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained the required starting material in 50% yield.

**CLAIMS**

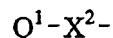
1. A quinoline derivative of the Formula I



- 5 wherein  $X^1$  is O or  $N(R^7)$  where  $R^7$  is hydrogen or (1-8C)alkyl;

$p$  is 0, 1, 2 or 3;

- each  $R^1$  group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, hydroxy, mercapto, amino, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or from a group of the formula :



wherein  $X^2$  is a direct bond or is selected from O, S, SO, SO<sub>2</sub>,  $N(R^8)$ , CO,  $CON(R^8)$ ,  $N(R^8)CO$ ,  $OC(R^8)_2$  and  $N(R^8)C(R^8)_2$ , wherein each  $R^8$  is hydrogen or (1-8C)alkyl, and  $Q^1$  is aryl,

- 15 aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl, (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocyclyl group within a  $R^1$  substituent optionally bears 1, 2 or 3 substituents, which may be the same or

- 20 different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-6C)alkyl]carbamoyl, 25 (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylureido,

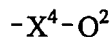
- 92 -

*N'*-(1-6C)alkylureido, *N',N'*-di-[(1-6C)alkyl]ureido, *N,N'*-di-[(1-6C)alkyl]ureido, *N,N',N'*-tri-[(1-6C)alkyl]ureido, *N*-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein  $X^3$  is a direct bond or is selected from O and N(R<sup>10</sup>), wherein R<sup>10</sup> is hydrogen or (1-8C)alkyl, and R<sup>9</sup> is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, mercapto-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, (1-6C)alkylsulphinyl-(1-6C)alkyl, (1-6C)alkylsulphonyl-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl,

10 (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, *N*-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl, ureido-(1-6C)alkyl, *N*-(1-6C)alkylureido-(1-6C)alkyl, *N'*-(1-6C)alkylureido-(1-6C)alkyl, *N',N'*-di-[(1-6C)alkyl]ureido-(1-6C)alkyl, *N,N'*-di-[(1-6C)alkyl]ureido-(1-6C)alkyl or *N,N',N'*-tri-[(1-6C)alkyl]ureido-(1-6C)alkyl, or  
15 from a group of the formula :



wherein  $X^4$  is a direct bond or is selected from O, CO and N(R<sup>11</sup>), wherein R<sup>11</sup> is hydrogen or (1-8C)alkyl, and Q<sup>2</sup> is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or  
20 different, selected from halogeno, hydroxy, (1-8C)alkyl and (1-6C)alkoxy,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R<sup>1</sup> optionally bears a (1-3C)alkylenedioxy group,

and wherein any heterocyclyl group within a R<sup>1</sup> substituent optionally bears 1 or 2 oxo or thioxo substituents,

25 and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more halogeno or (1-8C)alkyl substituents and/or a substituent selected from hydroxy, mercapto, amino, cyano, carboxy, carbamoyl, ureido, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl,  
30 *N,N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylureido, *N'*-(1-6C)alkylureido, *N',N'*-di-[(1-6C)alkyl]ureido, *N,N'*-di-[(1-6C)alkyl]ureido, *N,N',N'*-tri-[(1-6C)alkyl]ureido,

*N*-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a  $R^1$  substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO<sub>2</sub>,  
 5  $N(R^{12})$ , CO, CH(OR<sup>12</sup>), CON(R<sup>12</sup>),  $N(R^{12})$ CO,  $N(R^{12})$ CON(R<sup>12</sup>), SO<sub>2</sub> $N(R^{12})$ ,  $N(R^{12})$ SO<sub>2</sub>,  
 CH=CH and C≡C wherein  $R^{12}$  is hydrogen or (1-8C)alkyl, or, when the inserted group is  $N(R^{12})$ ,  $R^{12}$  may also be (2-6C)alkanoyl;

$q$  is 0, 1 or 2;

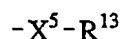
each  $R^2$  group, which may be the same or different, is selected from halogeno,  
 10 trifluoromethyl, cyano, hydroxy, amino, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl,  
 (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

$R^3$  is hydrogen, (1-8C)alkyl, (2-8C)alkenyl or (2-8C)alkynyl;

$R^4$  is hydrogen, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, halogeno-(1-6C)alkyl,  
 hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl,  
 15 amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl,  
 carbamoyl-(1-6C)alkyl, *N*-(1-6C)alkylcarbamoyl-(1-6C)alkyl, *N,N*-di-[(1-6C)alkyl]carbamoyl-  
 (1-6C)alkyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or  
*N*-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl;

or  $R^3$  and  $R^4$  together with the carbon atom to which they are attached form a  
 20 (3-8C)cycloalkyl group;

$R^5$  is hydrogen, (1-8C)alkyl, (2-8C)alkenyl or (2-8C)alkynyl or a group of the formula :



wherein  $X^5$  is a direct bond or is selected from O and  $N(R^{14})$ , wherein  $R^{14}$  is hydrogen or  
 (1-8C)alkyl, and  $R^{13}$  is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl  
 25 or cyano-(1-6C)alkyl;

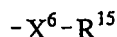
**Ring A** is a 6-membered monocyclic or a 10-membered bicyclic aryl ring or a  
 5- or 6-membered monocyclic or a 9- or 10-membered bicyclic heteroaryl ring with up to three  
 ring heteroatoms selected from oxygen, nitrogen and sulphur;

$r$  is 0, 1, 2 or 3; and

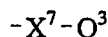
30 each  $R^6$  group, which may be the same or different, is selected from halogeno,  
 trifluoromethyl, cyano, hydroxy, mercapto, amino, carboxy, carbamoyl, sulphamoyl, ureido,  
 (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio,

- 94 -

- (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N'*-(1-6C)alkylureido, *N',N'*-di-[(1-6C)alkyl]ureido, *N*-(1-6C)alkylsulphamoyl,
- 5 *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



- wherein  $X^6$  is a direct bond or is selected from O and N( $R^{16}$ ), wherein  $R^{16}$  is hydrogen or (1-8C)alkyl, and  $R^{15}$  is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, mercapto-(1-6C)alkyl,
- 10 (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, (1-6C)alkylsulphinyl-(1-6C)alkyl, (1-6C)alkylsulphonyl-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, *N*-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, *N*-(1-6C)alkylcarbamoyl-
- 15 (1-6C)alkyl, *N,N*-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, sulphamoyl-(1-6C)alkyl, *N*-(1-6C)alkylsulphamoyl-(1-6C)alkyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl-(1-6C)alkyl, ureido-(1-6C)alkyl, *N*-(1-6C)alkylureido-(1-6C)alkyl, *N'*-(1-6C)alkylureido-(1-6C)alkyl, *N',N'*-di-[(1-6C)alkyl]ureido-(1-6C)alkyl, *N,N'*-di-[(1-6C)alkyl]ureido-(1-6C)alkyl, *N,N',N'*-tri-[(1-6C)alkyl]ureido-(1-6C)alkyl, (1-6C)alkanesulphonylamino-(1-6C)alkyl or
- 20 *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino-(1-6C)alkyl, or from a group of the formula :



- wherein  $X^7$  is a direct bond or is selected from O, S, SO, SO<sub>2</sub>, N( $R^{17}$ ), CO, CH(OR<sup>17</sup>), CON( $R^{17}$ ), N( $R^{17}$ )CO, N( $R^{17}$ )CON( $R^{17}$ ), SO<sub>2</sub>N( $R^{17}$ ), N( $R^{17}$ )SO<sub>2</sub>, C( $R^{17}$ )<sub>2</sub>O, C( $R^{17}$ )<sub>2</sub>S and C( $R^{17}$ )<sub>2</sub>N( $R^{17}$ ), wherein each  $R^{17}$  is hydrogen or (1-8C)alkyl, and  $Q^3$  is aryl, aryl-(1-6C)alkyl,
- 25 (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl, (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

- or two  $R^6$  groups together form a bivalent group that spans adjacent ring positions on Ring A selected from OC( $R^{18}$ )<sub>2</sub>O, OC( $R^{18}$ )<sub>2</sub>C( $R^{18}$ )<sub>2</sub>O, OC( $R^{18}$ )<sub>2</sub>C( $R^{18}$ )<sub>2</sub>, C( $R^{18}$ )<sub>2</sub>OC( $R^{18}$ )<sub>2</sub>, OC( $R^{18}$ )<sub>2</sub>N( $R^{19}$ ), N( $R^{19}$ )C( $R^{18}$ )<sub>2</sub>N( $R^{19}$ ), N( $R^{19}$ )C( $R^{18}$ )<sub>2</sub>C( $R^{18}$ )<sub>2</sub>, C( $R^{18}$ )<sub>2</sub>N( $R^{19}$ )C( $R^{18}$ )<sub>2</sub>,
- 30 CO.N( $R^{18}$ )C( $R^{18}$ )<sub>2</sub>, N( $R^{18}$ )CO.C( $R^{18}$ )<sub>2</sub>, N( $R^{19}$ )C( $R^{18}$ )<sub>2</sub>CO, CO.N( $R^{18}$ )CO, N( $R^{19}$ )N( $R^{18}$ )CO, N( $R^{18}$ )CO.N( $R^{18}$ ), O.CO.N( $R^{18}$ ), O.CO.C( $R^{18}$ )<sub>2</sub> and CO.OC( $R^{18}$ )<sub>2</sub> wherein each  $R^{18}$  is

- 95 -

hydrogen, (1-8C)alkyl, (2-8C)alkenyl or (2-8C)alkynyl, and wherein R<sup>19</sup> is hydrogen, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl or (2-6C)alkanoyl,

and wherein any aryl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocyclyl group within an R<sup>6</sup> group optionally bears 1, 2 or 3 substituents, which may be the same or  
 5 different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-6C)alkyl]carbamoyl,  
 10 (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N'*-(1-6C)alkylureido, *N',N'*-di-[(1-6C)alkyl]ureido, *N*-(1-6C)alkylureido, *N,N'*-di-[(1-6C)alkyl]ureido, *N,N',N'*-tri-[(1-6C)alkyl]ureido, *N*-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

15  $-X^8-R^{20}$

wherein X<sup>8</sup> is a direct bond or is selected from O and N(R<sup>21</sup>), wherein R<sup>21</sup> is hydrogen or (1-8C)alkyl, and R<sup>20</sup> is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, mercapto-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, (1-6C)alkylsulphinyl-(1-6C)alkyl, (1-6C)alkylsulphonyl-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl,  
 20 (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or *N*-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl, or from a group of the formula :

$-X^9-Q^4$

wherein X<sup>9</sup> is a direct bond or is selected from O, CO and N(R<sup>22</sup>), wherein R<sup>22</sup> is hydrogen or  
 25 (1-8C)alkyl, and Q<sup>4</sup> is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, hydroxy, (1-8C)alkyl and (1-6C)alkoxy,

and wherein any aryl, heteroaryl or heterocyclyl group within an R<sup>6</sup> group optionally bears a (1-3C)alkylenedioxy group,

30 and wherein any heterocyclyl group within an R<sup>6</sup> group optionally bears 1 or 2 oxo or thioxo substituents,

and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within an R<sup>6</sup> group optionally bears on each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more halogeno or (1-8C)alkyl substituents and/or a



- 96 -

- substituent selected from hydroxy, mercapto, amino, cyano, carboxy, carbamoyl, ureido, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, 5 (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N'*-(1-6C)alkylureido, *N',N'*-di-[(1-6C)alkyl]ureido, *N*-(1-6C)alkylureido, *N,N'*-di-[(1-6C)alkyl]ureido, *N,N',N'*-tri-[(1-6C)alkyl]ureido, *N*-(1-6C)alkylsulphamoyl, *N*-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino,
- 10 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within an R<sup>6</sup> group are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO<sub>2</sub>, N(R<sup>23</sup>), N(R<sup>23</sup>)CO, CON(R<sup>23</sup>), N(R<sup>23</sup>)CON(R<sup>23</sup>), CO, CH(OR<sup>23</sup>), N(R<sup>23</sup>)SO<sub>2</sub>, SO<sub>2</sub>N(R<sup>23</sup>), CH=CH and C≡C wherein R<sup>23</sup> is hydrogen or (1-8C)alkyl, or, when the inserted group is N(R<sup>23</sup>), R<sup>23</sup> may also be (2-6C)alkanoyl;
- 15 or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

2. A quinoline derivative of the Formula I according to claim 1 wherein p is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 6- and 7-positions and the R<sup>1</sup> group at the 6-position is selected from cyano, hydroxy, methoxy, ethoxy and propoxy, and 20 the R<sup>1</sup> group at the 7-position is selected from methoxy, ethoxy, propoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin- 25 4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 30 3-homopiperazin-1-ylpropoxy,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl,

- 97 -

hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally *N*-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl,  
 5 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,  
 and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 oxo substituents,  
 and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from  
 10 hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, *N*-ethyl-*N*-methylamino and *N*-isopropyl-*N*-methylamino.

3. A quinoline derivative of the Formula I according to claim 1 wherein Ring A is a 6-membered monocyclic aryl ring or a 5- or 6-membered monocyclic heteroaryl ring with up to  
 15 three ring heteroatoms selected from oxygen, nitrogen and sulphur.

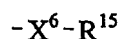
4. A quinoline derivative of the Formula I according to claim 1 wherein *r* is 1, 2 or 3 and each R<sup>6</sup> group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy,  
 20 (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoylamino and *N*-(1-6C)alkyl-(2-6C)alkanoylamino.

5. A quinoline derivative of the Formula I according to claim 1 wherein two R<sup>6</sup> groups together form a bivalent group that spans adjacent ring positions on Ring A selected from  
 25 OC(R<sup>18</sup>)<sub>2</sub>O, OC(R<sup>18</sup>)<sub>2</sub>C(R<sup>18</sup>)<sub>2</sub>, C(R<sup>18</sup>)<sub>2</sub>OC(R<sup>18</sup>)<sub>2</sub>, OC(R<sup>18</sup>)<sub>2</sub>N(R<sup>19</sup>), N(R<sup>19</sup>)C(R<sup>18</sup>)<sub>2</sub>N(R<sup>19</sup>), N(R<sup>19</sup>)C(R<sup>18</sup>)<sub>2</sub>C(R<sup>18</sup>)<sub>2</sub> and C(R<sup>18</sup>)<sub>2</sub>N(R<sup>19</sup>)C(R<sup>18</sup>)<sub>2</sub>, wherein each of R<sup>18</sup> and R<sup>19</sup> is hydrogen, (1-8C)alkyl, (2-8C)alkenyl or (2-8C)alkynyl.

6. A quinoline derivative of the Formula I according to claim 1 wherein :-  
 30 X<sup>1</sup> is O or NH;  
*p* is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 6- and 7-positions and the R<sup>1</sup> group at the 6-position is selected from cyano, hydroxy, methoxy, ethoxy and propoxy, and the R<sup>1</sup> group at the 7-position is selected from methoxy, ethoxy,

- 98 -

- propoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy,
- 5 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,
- 10 and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally *N*-substituted
- 15 with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,
- and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 oxo substituents,
- and wherein any CH, CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on
- 20 each said CH, CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, *N*-ethyl-*N*-methylamino and *N*-isopropyl-*N*-methylamino;
- q is 0 or q is 1 and the R<sup>2</sup> group is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino;
- 25 each of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is hydrogen;
- Ring A is a phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl ring; and
- r is 1 or 2 and one R<sup>6</sup> group is located at the 3- or 4-position (relative to the CON(R<sup>5</sup>) group), and each R<sup>6</sup> group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino,
- 30 or the first R<sup>6</sup> group is located at the 3- or 4-position (relative to the CON(R<sup>5</sup>) group) and is a group of the formula :



- 99 -

wherein  $X^6$  is a direct bond or O and  $R^{15}$  is hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 3-hydroxypropyl, cyanomethyl, 1-cyanoethyl, 2-cyanoethyl, 3-cyanopropyl, aminomethyl, 1-aminoethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 3-methylaminopropyl, dimethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, phenyl, benzyl, cyclopropyl, cyclopentyl, cyclohexyl, thienyl, imidazolyl, thiazolyl, thiadiazolyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, pyrrolidinylmethyl, 2-(pyrrolidinyl)ethyl, 3-(pyrrolidinyl)propyl, morpholinylmethyl, 2-(morpholinyl)ethyl, 3-(morpholinyl)propyl, piperidinylmethyl, 2-(piperidinyl)ethyl, 3-(piperidinyl)propyl, homopiperidinylmethyl, piperazinylmethyl, 2-(piperazinyl)ethyl, 3-(piperazinyl)propyl or homopiperazinylmethyl, provided that, when  $X^6$  is O, there are at least two carbon atoms between  $X^6$  and any heteroatom in the  $R^{15}$  group,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the  $R^6$  group optionally bears a substituent selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino and any such aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the  $R^6$  group optionally bears a further substituent selected from hydroxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl,

and any second  $R^6$  group that is present is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino; or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

7. A quinoline derivative of the Formula I according to claim 1 wherein :-

$X^1$  is O;

25 p is 2 and the first  $R^1$  group is a 6-cyano or 6-methoxy group and the second  $R^1$  group is located at the 7-position and is selected from methoxy, ethoxy and 2-methoxyethoxy;

q is 0;

each of  $R^3$ ,  $R^4$  and  $R^5$  is hydrogen;

Ring A is phenyl; and

30 r is 1 or 2 and one  $R^6$  group is located at the 3-position (relative to the  $CON(R^5)$  group), and each  $R^6$  group, which may be the same or different, is selected from fluoro, chloro, methoxy, methylamino and dimethylamino,

- 100 -

or the first R<sup>6</sup> group is located at the 3-position (relative to the CON(R<sup>5</sup>) group) and is selected from hydroxymethyl, 1-hydroxyethyl, aminomethyl, 1-aminoethyl, methylaminomethyl, 1-methylaminoethyl, dimethylaminomethyl and 1-dimethylaminoethyl, and any second R<sup>6</sup> group that is present is selected from fluoro, chloro, methoxy, methylamino and dimethylamino; or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

8. A quinoline derivative of the Formula I according to claim 1 wherein :-  
X<sup>1</sup> is O;  
p is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 6- and 7-positions and are selected from cyano, methoxy, ethoxy, propoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy and 2-(2-methoxyethoxy)ethoxy;  
q is 0 or q is 1 and the R<sup>2</sup> group is fluoro, chloro, methyl or methoxy;  
each of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is hydrogen;  
Ring A is phenyl; and  
r is 1 or 2 and the first R<sup>6</sup> group is located at the 3-position (relative to the CON(R<sup>5</sup>) group) and is selected from fluoro, chloro, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, cyclopropylamino, *N*-cyclopropyl-*N*-methylamino, hydroxymethyl, aminomethyl, methylaminomethyl, ethylaminomethyl, isopropylaminomethyl, cyclopropylaminomethyl, dimethylaminomethyl, diethylaminomethyl, *N*-ethyl-*N*-methylaminomethyl, *N*-cyclopropyl-*N*-methylaminomethyl, azetidinylmethyl, pyrrolidinylmethyl, morpholinylmethyl, piperidinylmethyl, homopiperidinylmethyl, piperazinylmethyl and homopiperazinylmethyl, and any second R<sup>6</sup> group that is present is selected from fluoro, chloro, methyl, ethyl, methoxy and ethoxy, and wherein any heterocyclyl group within the R<sup>6</sup> group optionally bears a methyl, ethyl or hydroxymethyl substituent; or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

30

9. A quinoline derivative of the Formula I according to claim 1 wherein :-  
X<sup>1</sup> is O;

- 101 -

p is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 6- and 7-positions and are selected from cyano, methoxy, ethoxy, propoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy and 2-(2-methoxyethoxy)ethoxy;

5 q is 0 or q is 1 and the R<sup>2</sup> group is fluoro, chloro, methyl or methoxy;  
each of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is hydrogen;

Ring A is pyridyl; and

r is 0, 1 or 2 and each R<sup>6</sup> group that is present is selected from fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, propyl, isopropyl, *tert*-butyl, cyclopropyl, cyclobutyl, 10 cyclopentyl, methoxy, ethoxy, methylamino, ethylamino, propylamino, isopropylamino, cyclopropylamino, 2-hydroxyethylamino, 2-methoxyethylamino, dimethylamino, *N*-cyclopropyl-*N*-methylamino, acetyl, hydroxymethyl, aminomethyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, isopropylaminomethyl, cyclopropylaminomethyl, dimethylaminomethyl, diethylaminomethyl, *N*-ethyl-*N*-methylaminomethyl, *N*-cyclopropyl-  
15 *N*-methylaminomethyl, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, pyrrolidin-1-ylmethyl, morpholinomethyl, piperidinomethyl and piperazin-1-ylmethyl,  
and wherein any heterocyclyl group within the R<sup>6</sup> group optionally bears a methyl or ethyl substituent;  
or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

20

10. A quinoline derivative of the Formula I according to claim 1 wherein :-

X<sup>1</sup> is O;

p is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 6- and 7-positions and are selected from cyano, methoxy, ethoxy, propoxy, 2-hydroxyethoxy, 25 3-hydroxypropoxy, 2-methoxyethoxy, 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy and 2-(2-methoxyethoxy)ethoxy;

q is 0 or q is 1 and the R<sup>2</sup> group is fluoro, chloro, methyl or methoxy;  
each of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is hydrogen;

Ring A is selected from thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl and 30 pyrazolyl; and

r is 0, 1 or 2 and each R<sup>6</sup> group that is present is selected from fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, propyl, isopropyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, methylamino, ethylamino, propylamino, isopropylamino,

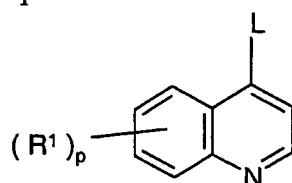
- 102 -

cyclopropylamino, 2-hydroxyethylamino, 2-methoxyethylamino, dimethylamino, *N*-cyclopropyl-*N*-methylamino, acetyl, hydroxymethyl, aminomethyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, isopropylaminomethyl, cyclopropylaminomethyl, dimethylaminomethyl, diethylaminomethyl, *N*-ethyl-*N*-methylaminomethyl, *N*-cyclopropyl-*N*-methylaminomethyl, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, pyrrolidin-1-ylmethyl, morpholinomethyl, piperidinomethyl and piperazin-1-ylmethyl, and wherein any heterocyclyl group within the R<sup>6</sup> group optionally bears a methyl or ethyl substituent; or a pharmaceutically-acceptable salt, solvate or pro-drug thereof.

10

11. A process for the preparation of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, according to claim 1 which comprises :-

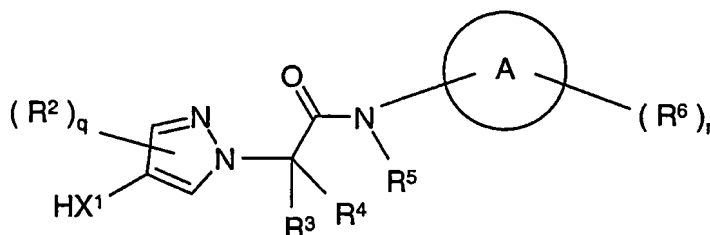
(a) the reaction of a quinoline of the Formula II



II

15

wherein L is a displaceable group and p and R<sup>1</sup> have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with a pyrazole of the Formula III



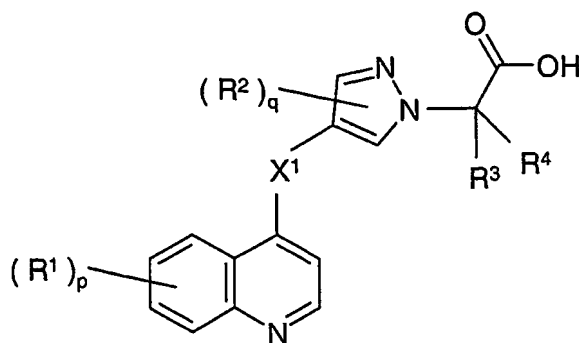
III

wherein X<sup>1</sup>, q, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, Ring A, r and R<sup>6</sup> have any of the meanings defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed;

20

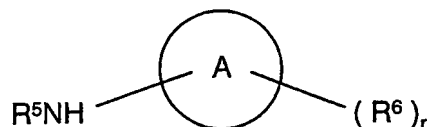
(b) the coupling of a quinoline of the Formula VII

- 103 -



VII

or a reactive derivative thereof, wherein  $p$ ,  $R^1$ ,  $X^1$ ,  $q$ ,  $R^2$ ,  $R^3$  and  $R^4$  have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with an amine of the Formula VI



VI

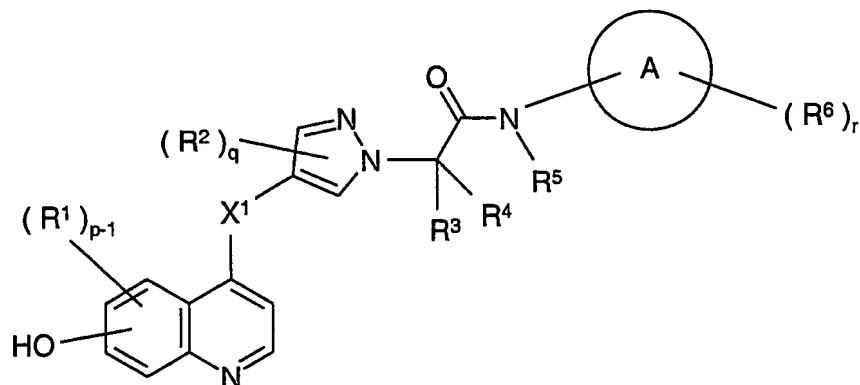
wherein  $R^5$ , Ring A,  $r$  and  $R^7$  have any of the meanings defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed;

(c) for the production of those compounds of the Formula I wherein at least one  $R^1$  group is a group of the formula



wherein  $Q^1$  is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group or an optionally substituted alkyl group and  $X^2$  is an oxygen atom, the coupling of a quinoline of the

Formula VIII



VIII



wherein each of p, R<sup>1</sup>, X<sup>1</sup>, q, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, Ring A, r and R<sup>6</sup> has any of the meanings defined in claim 1 except that any functional group is protected if necessary, with an appropriate alcohol wherein any functional group is protected if necessary, whereafter any protecting group that is present is removed;

- 5 (d) for the production of those compounds of the Formula I wherein a R<sup>6</sup> group is a group of the formula -X<sup>6</sup>-R<sup>15</sup> wherein X<sup>6</sup> has any of the meanings defined in claim 1 and R<sup>15</sup> is an amino-substituted (1-6C)alkyl group, the reaction of a compound of the Formula I wherein a R<sup>6</sup> group is a group of the formula -X<sup>6</sup>-R<sup>15</sup> wherein R<sup>15</sup> is a halogeno-substituted (1-6C)alkyl group with an appropriate amine or with a nitrogen-containing heterocyclyl compound; or
- 10 (e) for the production of those compounds of the Formula I wherein a R<sup>6</sup> group is a group of the formula -X<sup>6</sup>-R<sup>15</sup> wherein X<sup>6</sup> has any of the meanings defined in claim 1 and R<sup>15</sup> is an amino-substituted (1-6C)alkyl group, the reductive amination of a compound of the Formula I wherein a R<sup>6</sup> group is a group of the formula -X<sup>6</sup>-R<sup>15</sup> wherein R<sup>15</sup> is a formyl or (2-6C)alkanoyl group;

- 15 and when a pharmaceutically-acceptable salt of a quinoline derivative of the Formula I is required, it may be obtained by reaction of said quinoline derivative with a suitable acid;  
and when a pharmaceutically-acceptable pro-drug of a quinoline derivative of the Formula I is required, it may be obtained using a conventional procedure.

- 20 12. A pharmaceutical composition which comprises a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, according to claim 1 in association with a pharmaceutically-acceptable diluent or carrier.

13. The use of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable  
25 salt, solvate or pro-drug thereof, according to claim 1 in the manufacture of a medicament for use in the treatment of cell proliferative disorders or in the treatment of disease states associated with angiogenesis and/or vascular permeability.

14. A method for the treatment of cell proliferative disorders in a warm-blooded animal in  
30 need of such treatment or for the treatment of disease states associated with angiogenesis and/or vascular permeability in a warm-blooded animal in need of such treatment which comprises administering to said animal an effective amount of a quinoline derivative of the

- 105 -

Formula I, or a pharmaceutically-acceptable salt, solvate or pro-drug thereof, according to claim 1.

# INTERNATIONAL SEARCH REPORT

Inte | Application No  
PC 1 / 002005/003856

A. CLASSIFICATION OF SUBJECT MATTER  
C07D401/12 C07D401/14 A61K31/506 A61K31/415 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	WO 2004/094410 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; HERON, NICOLA, MURDOCH; PASQUE) 4 November 2004 (2004-11-04) cited in the application page 1, line 3 - page 1, line 6; claims; examples	1-14
A	WO 02/00649 A (ASTRAZENECA AB; MORTLOCK, ANDREW; JUNG, FREDERIC) 3 January 2002 (2002-01-03) cited in the application page 1, line 3 - page 1, line 7; claims; examples	1-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

9 December 2005

Date of mailing of the international search report

22/12/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Schmid, A

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB2005/003856

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claim 14 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Inte Application No  
PC 1 / 002005/003856

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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